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CHANGES IN SENSORY ADAPTATION TIME AND AFTER-SENSATION WITH LESIONS OF PARIETAL LOBE

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PATHOLOGIC conditions frequently produce symptoms which are reflections of normal functions. This has been affirmed repeatedly by various authors. One of the normal functions which has thus been elicited in patients with injuries to the brain is rivalry with resultant dominance of strong over weak sensation. The process of rivalry with resultant dominance was recently demonstrated in patients with defects in the visual and cutaneous spheres.[1] Visual perception, diminished in a given area owing to a lesion in the optic pathway, can be further reduced or made totally extinct when stimuli (objects) are exposed simultaneously in the normal and in the affected field of vision. This visual extinction was explained by Poppelreuter as due to inattention.[2] However, a careful study of patients manifesting this phenomenon has thrown doubt on Poppelreuter's theory, for several reasons: (*a*) The extinction occurs in spite of the patient's attempt to concentrate on the object in the affected field. (*b*) The phenomenon is sometimes found to be limited to homonymous quadrants. Certainly, it would be difficult for one to lose attention in one and not in the other quadrant of a homonymous half-field of vision. (*c*) The extinction is sometimes incomplete, being manifest in the form of a reduction of visual perception. This reduction may range from fluctuation to almost complete obscuration of the exposed image, the amount depending to some extent on the degree of stimulation in the normal field of vision. The fact that some visual

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1. (*a*) Bender, M. B., and Furlow, L. T.: Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, Arch. Neurol. & Psychiat. **53**:29-33 (Jan.) 1945. (*b*) Bender, M. B.: Extinction and Precipitation of Cutaneous Sensations, ibid. **54**:1-10 (July) 1945.

2. Poppelreuter, W.: Die psychischen Schädigungen durch Kopfschuss im Kriege 1914-1916: Die Störungen der niederen und höheren Sehleistungen durch Verletzungen des Okzipitalhirns, Leipzig, Leopold Voss, 1917, vol. 1.

perception is preserved in the affected field indicates that the patient is paying attention. The indistinctness of the exposed image must therefore be due to other factors. (*d*) The phenomenon is not present with very rapid exposures of the objects in both fields of vision. In fact, in these circumstances the patient may actually see more than his plotted field of vision would indicate.[3]

Similarly, studies in cutaneous perception with the method of double and simultaneous stimulation may reveal varying degrees of reduced sensibility on the affected side, whereas single stimulation may show no such reduction.[1b] Again, under these conditions there is a variety of alterations in cutaneous perception which seem to form a continuum: from an elevation of threshold through fluctuation, dulling and reduction of adaptation time to complete abolition of sensation. Here, too, it would be difficult to account for the reduction or extinction of cutaneous perception on the basis of inattention. All these observations seem to refute Poppelreuter's hypothesis. To be sure, attention is a factor in the ability to perceive: Newhall,[4] in controlled experiments, found that the closer the attention the better discrimination there is between faint visual stimuli. Furthermore, Hardy, Wolff and Goodell [5] asserted that distraction, attitude and suggestion may modify the threshold for pain.

Besides the mechanism of rivalry with resultant dominance of one sensation over another, there are other processes which participate in the elaboration of a sensation or percept. Sensory adaptation and after-sensation are two such processes, which will be considered in this communication.

Psychologically speaking, sensations in nearly all modalities show the phenomenon of negative adaptation. That is, under continual and unchanging application of a given stimulus the characteristic sensation evoked disappears after a given interval. This interval is known as the sensory adaptation time.

As used in this paper, the term "adaptation" is taken from the language of the experimental psychologist. It is realized that the psychologist tends to analyze sensory adaptation in terms of function within the peripheral end organ. Similarly, the physiologist tries to relate adaptation at the receptor level to the refractory stages in conduction of nerve fibers.[6] However, it is difficult to interpret a subject's report of changes in perception (adaptation) from the standpoint of the peripheral

3. Bender, M. B., and Teuber, H. L.: Phenomena of Fluctuation, Extinction and Completion Associated with Visual Perception, Arch. Neurol. & Psychiat., to be published.

4. Newhall, S. M.: Effects of Attention on the Intensity of Cutaneous Presence and Visual Brightness, Arch. Psychol. (no. 61) **9**:1-75, 1923.

5. Hardy, J. D.; Wolff, H. G., and Goodell, H.: The Pain Threshold in Man, A. Research Nerv. & Ment. Dis., Proc. (1942) **23**:1-15, 1943.

end organ alone. In response to a stimulus all levels of the nervous system are activated, and the cortex must be considered as one of the substrates in which adaptation occurs. In this communication, therefore, adaptation is used in an empiric (clinical) sense; that is, the patient's reports of the presence or absence of a given sensation are recorded verbatim. When the patient states that he no longer feels a given stimulus, it is implied that adaptation is complete. Although adaptation of necessity involves the peripheral level, the pathologic material to be presented here illustrates the less explored role played by the cerebral cortex.

Closely related to the adaptation mechanism is the phenomenon of after-sensation. After-sensation is a reaction found on the removal of a cutaneous stimulus and is analogous to the visual after-image. As a rule, an after-sensation lasts a few seconds, the duration depending on the intensity of the stimulus applied. Often it is not recognized unless the subject's attention is called to it. The duration of the after-sensation varies from one person to another, but there is no notable difference between corresponding points on the two sides of the body.

Alterations, especially reduction in sensory adaptation time, are commonly found in persons with defective sensation. In a large series of patients with battle wounds involving various parts of the sensory nervous system (observed at a Naval hospital during 1944), special studies on sensory adaptation and after-sensation were made. In evaluation of changes in sensory adaptation and after-sensation in the affected area, the normal zones were compared as a control. Nearly all these patients exhibited a reduction of the adaptation times for pain, touch and temperature sensations.[1b] After-sensation was also diminished or abolished. The most pronounced reduction in adaptation time was apparent in cases in which there were lesions of the parietal lobe. In 1 patient this was so extreme and involved so many modalities that it caused him discomfort and, at least in one instance, embarrassment.

REPORT OF CASES

CASE 1.[7]—A Marine aged 29 was wounded in the right side of the head but was not incapacitated until a missile struck him in the left occipitoparietal region, when he fell unconscious. On regaining consciousness, he found himself in a dugout, unable to speak or to move the right side of the body. He was evacuated to the hospital. On examination, global aphasia, right hemiplegia and apparent hemianopsia were noted. One week later the hemiplegia had disappeared. A craniotomy was then performed, and fragments of bone were removed from the left side of the head. The underlying occipitoparietal cortex was

6. This school of thought is represented by Adrian (Adrian, E.: The Basis of Sensation, New York, W. W. Norton & Company, 1928).

7. This case was previously described from the standpoint of visual extinction.[1a] Some of the content is therefore to be repeated in this report.

contused. The patient continued to improve. Within a month the hemianopsia began to recede, and he became more communicative. However, the following significant symptoms lingered during the next two months: (*a*) striking acalculia, (*b*) spelling defect, (*c*) dysgraphia and (*d*) inability to perceive an object on the right when a concomitant stimulus was present in the left field of vision. Spontaneous speech returned. He showed little agrammatism and no anomia. There was no finger agnosia or disorientation for right and left. His greatest defect was in calculation. He had always considered himself good in arithmetic, but twelve weeks after the injury he still was unable to recite the multiplication tables of 2's and 3's accurately. He made errors in simple tests, such as 8 + 3, and other sums which equated to less than 20. The defect in calculation was greatest for subtraction. Often he was unable to recognize the correct solution to the problem, even when it was given him, and he was seldom certain of the answer.

Visual Disturbances.—Ever since the hemianopsia had begun to recede, the patient complained, "If I stare long enough, my vision starts to blur on the right side. I can't go to the picture show for the same reason. When I first start to read, everything is clear; but then I must stop because the right side blurs. After a rest I can see again. Also, if I look at one object long enough and look away, I still can see it." The last phenomenon was present for one month. Examination revealed that the patient was unable to see in the right homonymous field when an object was exposed simultaneously in the left field of vision. This was true with both uniocular and binocular testing. When the perimetric fields became normal (the last defect noted was that for color in the right inferior quadrant), this phenomenon became most apparent. While he was fixing on a central point, the patient clearly perceived the form and color of an object placed in the right field of vision. However, when another object was brought into view on his left side, the image on the right became extinct. This extinction phenomenon was noted on repeated examinations in the right homonymous fields of vision. During the extinction of the image the patient made a strong effort to "see" the object by squinting his eyes and concentrating but was unsuccessful. However, as soon as the stimulus in the left field was removed, he perceived the exposed object on the right. When tested for separately, the object on the right appeared clear but sometimes blurred and dull. The object seemed to fluctuate in distinctness.

In time the remaining aphasic symptoms decreased further, although the acalculia was still striking. The visual phenomenon began to change. Fourteen weeks after the injury it was noted that the image in the right field did not always vanish when the left field was stimulated. Instead, it became dull, lost its form and color and appeared shadowy. There was no micropsia or teleopsia. Again, when the stimulus in the left field of vision was removed, the object on the right became more luminous and regained its color and meaning. This was noted irrespective of the degree of likeness or unlikeness in luminosity of the objects exposed in the opposite fields of vision. There was no apparent loss of attention. What there seemed to be was a relative reduction of visual acuity or a dimming of the visual image. These phenomena were less apparent the nearer the object in the right field was exposed to the point of fixation.

Sixteen weeks after the injury the following observations were noted: (*a*) On separate tests of all four quadrants, the patient stated that the image in the right superior homonymous field of vision was clearer than that in the right inferior homonymous field. (*b*) The dimming of the image was much more apparent in the inferior than in the superior quadrant on the right side. Thus,

when a pencil was placed in the patient's right inferior field, he recognized it, but when another pencil was placed in the left inferior field, the one on the right became blurred, dull and shadowy. The same was true when the corresponding superior quadrants were tested, but the difference here was much less apparent than in the comparable lower quadrants. When a long pencil was held vertically in the right field of vision, the patient stated he perceived that part of the pencil in the upper quadrant more clearly than the portion in the lower quadrant. The simultaneous exposure of an object in the same position on the left side produced a further decrease of perception on the right side, particularly in the lower quadrant.

Sensory Disturbances.—Five months after the injury the patient returned from a forty day furlough and complained that he did not know what his right hand was doing. He described the following embarrassing situation: "I was sitting in the parlor with my right hand around my girl. Her mother was sitting opposite us. Suddenly I noticed a change in the mother's facial expression. She seemed uneasy and disturbed by something. So did my girl. When I looked to the right, I found that my right hand had dropped down to the girl's breast. I quickly straightened out and apologized. At the same time, I could not understand how it happened that I was not aware of my hand. Since then I have tested myself and find that I lose feeling in this hand very quickly. It goes dead. If I look at it, or if I make a strong movement, then the feeling in the hand comes back. Sometimes, I think I have only one hand." [8] Subsequently, he became more conscious of this symptom in other forms. Thus, when he reached for a tray of food, he almost tore his pocket open because he was unaware of the fact that his right hand was in the pocket. This loss of awareness of the right hand recurred frequently. Sometimes, he unconsciously dropped a cigaret which he held in his right hand. Not infrequently he was surprised to find this limb in a position which he could not recall having assumed. When he hesitated for several seconds while writing, he found that he could not feel the pencil in his hand unless he looked at it. For this reason, he could not write legibly. If he did not scrutinize them carefully, the lines which he wrote became crooked, even on ruled paper.

Sensory Examinations.[9]—Pain: Sensation of 2.5 to 15 Gm. weights with a no. 10 needle point applied to different areas of the skin seemed to be preserved on the right side when tested for separately and compared with sensation on the left. However, when the left and the right hand were stimulated simultaneously, he felt pain more keenly on the left side. On the right side the sensation of pain disappeared rapidly, and during this phase it fluctuated in intensity. It then changed to a

8. It is interesting that the patient became aware of trouble with his right hand during an embarrassing situation. This suggests that the new symptoms were psychogenic (conversion phenomena). Psychiatrically, it might be argued that the patient freed himself of all blame for the parlor incident by accusing his formerly paralyzed hand of doing things without his knowledge. Although one cannot deny that the accidental shifting of his right hand to the girl's breast was due to a subconscious libidinal force, subsequent neurologic and special studies will reveal that his act was most probably the result of organic defects in sensation (reduction of adaptation time with consequent impairment of kinesthesis). Nevertheless, it was emotional stress which precipitated the latent sensory defects. The case illustrates the close relationship between the psychogenic and the organic components of symptoms.

9. The method employed in eliciting the sensory status was the same as that described in a previous communication.[1b]

sensation of pressure and ultimately disappeared altogether. The time for the disappearance of a sensation produced by a 5 Gm. needle point stimulus was 12 seconds on the right hand and well over 70 seconds at the corresponding point on the left hand. Foci on the rest of the right upper extremity showed similar reductions of sensory adaptation time, but the reduction was most pronounced in the distal portion. A slight decrease in adaptation time was also noted over the trunk and the lower extremity on the right side.[10] After-sensation for this modality was either absent or much diminished on the right side of the body, especially in the hand.

Temperature Sensation: The adaptation for temperature sensation was much reduced in the right hand. Thus, when identical objects were held in the hands, with the hand on the right he perceived a change in temperature within 5 to 7 seconds, while with the left hand he did not sense a change until after 15 seconds.

When both hands were placed in warm water (115 F.), the sensation of warmth or heat rapidly disappeared (within 5 seconds) in the right hand, whereas it lingered for a long period in the left hand. The change occurred first at the wrist and spread to the finger tips. The temperature sensation disappeared last in the right index finger. At the time the sensation of heat became extinct the sensation of wetness disappeared. In fact, after 10 seconds the patient was uncertain whether his right hand was in the bowl of water at all when his eyes were closed.

Touch and Deep Pressure Sensation: The adaptation time for superficial touch as well as deep pressure sensation was much reduced in the right hand, the sensation disappearing completely within 5 to 10 seconds. The sensation on the left side lasted from 30 to well over 80 seconds. These changes were well illustrated by the tests made for stereognosis.

Stereognosis: The patient immediately recognized the shape, size and texture of any object placed either in the right or in the left hand or simultaneously in the two hands. With his eyes closed he felt and correctly identified a pencil held in his right hand; but when he held the pencil still, it seemed to him to have disappeared after an interval of 7 seconds. The same was true for larger and heavier objects, such as a comb, a fork and a box of matches. The duration of the "adaptation time" for these was longer than for lighter and smaller objects.[11] Stereognosis in the left hand was normal, and he could recognize the presence of an object even after holding it for over 3 minutes.

Barognosis: Weights were easily differentiated when placed in each hand separately or in the two hands simultaneously, but after a few seconds barog-

10. Since the patient's sensory complaints were confined to the right hand, most of the special tests for adaptation time were made chiefly on the right limb and the results compared with those for the left. Differences in pain sensation between the two sides of the body were found elsewhere; but since these were not conspicuous, similar tests for other modalities were not made in every part of the body to the same extent and in the same detail as for pain. Henceforth, comparisons made in places other than in the hand will not be reported unless the changes found were significantly different than those reported for pain sensation.

11. It is fully realized that one cannot speak of a true adaptation for stereognosis or other complex perceptions with the same connotation as for simple pain or pressure sensation. The probability is that adaptation for the primary modalities took place first, and once these sensations disappeared the patient could no longer perceive the object held in his hand. Nevertheless, it is possible that there may be adaptation for the stereognostic sense per se.

nosis became defective in the right hand. Identical (480 Gm.) oblong weights placed in each hand felt the same, but after a few seconds (table 1) there was a change. The object on the right became lighter than that on the left, and later the sensation of its presence seemed to have disappeared altogether. Not only did the object seem to vanish, but his hand and forearm felt as though they were not there.

When this experiment was repeated and continued for a much longer period, the patient showed the same reactions. At the end of 3 minutes, although he had no sensation of a hand, of a forearm or of the weight which he held, he began to notice a peculiar pulling pain in the elbow region, "as though the cords were pulling there." This was the first subjective sign of fatigue in the right upper extremity in contrast to the left hand, which began to tire 2 minutes after the weight had been put on.

Kinesthesia: As already mentioned, the patient complained of loss of sense of position of the limb in space after a relatively short interval. Recognition of

TABLE 1.—*Time Elapsed After 480 Gm. Weights Were Placed Simultaneously in the Hands with the Patient's Eyes Closed*

Time, Sec.	Right	Left
7	Sensation is decreasing	Stereognosis and other sensations preserved
19	Patient barely feels touch or outline of square weight in hand	No change
37	Hand seems to have disappeared	Hand is felt in outstretched position
40	Weight is lighter in right than in left hand; sensation of weight is felt at wrist and elbow; rest of extremity is not felt	No change
65	No sensation of temperature; right hand moved up spontaneously above left; weight is lighter than that in left hand	No change; possibly left hand is moved down lower than right; patient is not aware of difference in position of outstretched hands, which is about 4 inches (10 cm.)
120	Patient is unable to determine shape or size of weight; no sense of fatigue as yet; weight feels lighter than that on left hand even after patient looks at object and moves it up and down	Patient still can recognize object with left hand, which feels tired and heavy at wrist and elbow

initiation of movement or passive motion was normal throughout. The sense of position of a digit, the forearm or arm or of parts of the lower extremity in space was also found to be normal. However, once the finger or any other part of the upper extremity had assumed a given posture and the patient was instructed to close his eyes and not to move his limbs, the ability to recognize the fixed posture or position in space of the right hand was lost after 7 seconds or more. Thus, when he held both upper extremities in the extended position above the head, after 7 seconds he complained that the feeling was "leaving" in his right arm and that this peculiar awareness of the absence of the limb spread distally toward the forearm within 10 to 12 seconds. Finally, he felt the absence of the right hand and forearm and said it was a sensation "as if they were not there."

On raising both feet in the air with his eyes closed, he noted after an interval of 10 seconds that the left lower extremity was still there but that he hardly felt the presence of the right leg and foot. He realized that the foot was there, but only because there was the weight of the shoe. (Symptomatically, the patient complained of frequent tripping with his right foot.)

On occasions when he was distracted by a conversation, he was suddenly asked to describe the location and posture of the right upper extremity without moving or looking at the affected limb. He then found he could not locate or describe the posture of the right arm, forearm or hand. He realized he possessed an arm and hand, but he could not locate them in space. Once, he thought the extremity was elevated to table level, but actually it was hanging limply at his side; his left arm was raised, and he identified this correctly. Initial two point discrimination and vibration sense appeared to be intact.

Graphesthesia: This modality was impaired in the right hand when the left hand was simultaneously stimulated with a painful stimulus. In fact, with simultaneous double stimulation on the two sides of the body and at corresponding points, almost all modalities showed a reduction in adaptation time on the right side, especially in the right upper extremity. This reduction was more conspicuous than the results obtained with single stimulation.

Spontaneous arm movements were diminished on the right. Although the patient was right handed, he invariably pointed and gesticulated with, and seemed to prefer, his left hand in everyday activity. The motor power was normal.

The patient was studied for several months. He continued to show this reduction in adaptation time for almost all modalities, especially in the right upper extremity. He was discharged from the service; and when he wrote one year later he reported no change in his subjective status.

Comment.—This case illustrates at least three mechanisms which participate in perception under pathologic conditions: (*a*) rivalry and dominance (manifested by the phenomenon of visual extinction); (*b*) adaptation to sensory stimuli (made apparent by reduction of adaptation time and consequent disturbances in cutaneous and kinesthetic perceptions) and (*c*) dynamic organization of body sensations into a scheme (particularly evident when his sense of position of a limb in space became defective as a result of reduced adaptation time). *Pari passu* with reduction in adaptation time, there were a loss of sense of position and a gain of the illusion that a limb was missing.[12] Evidently, the patient had a

12. Head (Studies in Neurology, London, Oxford University Press, 1920, pp. 779-789), in his studies on sensation, described several cases in which the patient complained of a sensation of missing part of a limb. One of them, with a gunshot wound implicating the left frontal and parietal lobes, complained two years after the injury that when he awakened at night he sometimes felt as though the last three fingers of his right hand were missing, that the whole hand seemed to disappear and that he had to move the fingers to make them "come to" again. Another patient, with a bullet wound of the right parietal cortex, complained three months after the injury that when he awakened at night he felt as though he had lost two or three fingers and that it seemed as though "this part of the left hand was gone altogether." Although these cases are not ideal examples of reduction in adaptation time, they illustrate a form of autotopagnosia, probably due to impairment of kinesthesia. The fact that movement caused return of sensation of a limb suggests that the disturbance in the body image in these cases was the result of an altered adaptation mechanism.

disorder in the body image or postural model of the body.[13] The disturbance in body scheme was transient and reversible. It appeared only when sensation in general became defective as result of impairment of the adaptation mechanism and disappeared whenever he moved, touched or looked at the affected limb.[14]

Underlying most of the sensory (cutaneous and kinesthetic) disturbances was the reduction of adaptation time. These changes were probably not due to fatigue, because (*a*) the removal of a stimulus from a cutaneous focus which became insentient with adaptation sometimes evoked an after-sensation and (*b*) the immediate reapplication of a stimulus at the same focus was quickly appreciated.

All the symptoms were most profound in the right upper extremity, especially in the distal portions. They all became manifest only after an interval which corresponded to a reduced adaptation interval.

The decrease in adaptation time became more apparent with simultaneous double stimulation. Some sensory disturbances were frequently found in patients with lesions of the parietal lobe, particularly on bilateral stimulation, but rarely to the degree found in this patient. Evidently, lesions of the parietal lobe can reduce sensory adaptation time.

Associated with a reduction in adaptation time in these patients was a decrease or abolition of the after-sensation.[1b] A decrease in after-sensation per se did not seem to produce symptoms. These patients had no complaints in that respect.

As already mentioned, not all patients with disease of the cortex and sensory pathways showed a decrease in adaptation time or in duration of after-sensation. Some of them showed what seemed to be an increase. Prolongation of after-sensation was often marked and more conspicuous than increase in duration of adaptation. With these changes there was usually an increased sensitivity to painful stimuli, and this was the chief basis for the patient's complaints.

The following case is illustrative of changes in after-sensation and adaptation time in a patient with injury to the anterior portion of the parietal lobe.

CASE 2.—A 22 year old Marine, private first class, sustained a gutter type of bullet wound in the left superior frontoparietal area on March 6, 1945. As soon as he was hit, he had the strange sensation that the right side of his body was

13. Riddoch, G.: Phantom Limbs and Body Shape, Brain **64**:197-222, 1941. Schilder, P.: The Image and the Appearance of the Human Body, Psyche Monographs 4, London, Kegan, Paul, Trench, Trubner & Co., Ltd., 1935.

14. The state of being adapted to a continuous stimulus may be terminated by the addition of a new stimulus (which, of necessity, alters the total stimulus configuration). When the patient looked at, moved or touched the affected hand, a change in the stimulus situation was inevitable. With this there followed a restoration of the original perceptive state and, consequently, of the body image.

spinning, but not the left side. A few moments later the right arm and leg twitched and soon felt "dead." Then he found he could not speak, although he knew what he wanted to say. He was given emergency treatment and evacuated to a hospital. Within two days the paralysis and numbness on the right side began to recede, and speech began to improve. A roentgenogram of the skull revealed two lines of fracture involving the left parietal bone.

The patient continued to improve and seemed to do well until June 17, when he had a right-sided convulsion. This, again, was preceded by a spinning sensation on the right side of the body and face. On several occasions he noticed tingling in the right lower part of the leg, but as a rule he had the sensation of "a rubber stocking dressed over this limb." The following week he had another attack, which began with twitching in the right arm. This was soon followed by paralysis, and with this he had a sensation of rapid whirling and revolving of the arm, even when the extremity was still. Neurologic examination on June 25 disclosed nothing of significance except for residual motor aphasia and some changes in the sensory spheres. When he was examined with single stimuli, the sensory status appeared to be normal; but when he was tested with simultaneous bilateral painful stimuli, there was slight dulling on the right side of the body. Light rubbing on the lateral side of the right calf yielded a sensation of tingling. All other sensations, including those elicited on special visual examinations, were practically normal. A pneumoencephalogram at this time revealed moderate dilatation of the ventricular system, especially of the left lateral ventricle.

Within the next three weeks the patient had five more seizures on the right side, and, except for a sensation of falling to the right, the whirling and spinning sensations were no longer present.

On July 4 an osteoplastic flap was raised for resection of scar tissue and adhesions. The left frontoparietal bone near the sagittal suture was found to be soft and the underlying brain tissue degenerated. After this, he went home on convalescent leave for thirty-five days, and when he returned he felt somewhat improved. His speech was less hesitant, and the peculiar paresthesias in the right leg had disappeared.

Special Sensory Examinations (Sept. 6, 1945).—1. Pain Sensation: Routine examination with single stimuli, such as the prick of a pin, produced sensations which were apparently of equal intensity throughout the body. However, with application of graduated stimuli measurement of duration of after-sensation and adaptation time showed a difference. There was a distinct abnormality on the right side, especially in the limbs. The sensory disturbances about to be described were most profound in the distal portions of the extremities.

(*a*) Stimulation on right side. A 2.5 Gm. weight stimulus with a no. 10 needle point applied continuously on the dorsum of the distal phalanx of the right index finger just below the finger nail produced a series of sensations, from that of a point to that of pressure, at the end of 40 seconds. This sensation of pressure changed back to sensation of pain within 75 seconds. The pain was dull and increased in severity within 110 seconds. This sensation fluctuated in intensity and remained throughout the period of application of the stimulus, which was 362 seconds. When the stimulus was removed, the patient insisted that the "pin" was still there and that it was painful. At this time he also volunteered the information that the "pin" was moved farther down (distally) toward the tip and that he could feel the needle track for about ¼ inch (0.6 cm.). The after-sensations (those of a "pin," pain and pressure) were present for over 5 minutes.

(*b*) Stimulation of left side. The same type of stimulus applied to the corresponding point on the left side produced a change from sensation of a point to that of pressure within 40 seconds. The pressure disappeared entirely at the end of 100 seconds. Removal of the stimulus produced a slight pricking sensation, which lasted 5 seconds.

(*c*) Bilateral simultaneous stimulation. On double simultaneous stimulation of these foci with 2.5 Gm. weights, there was a sensation of pain on both sides. Sensation on both sides became weak within 25 seconds; that on the left changed to a sensation of pressure within 40 seconds, and became faint and almost disappeared within 105 seconds. On the right, the sensation of pain persisted, as well as the sensation of a "pin." However, the sensation of pain on the right fluctuated and changed to a sensation of pressure and of dull pain. The latter sensations continued to fluctuate for over 4 minutes. When the stimuli were removed, the patient felt the "pin" again on each side, but the sensation on the right was more painful. The after-sensation on the right lasted well over 2 minutes, while that on the left was present for 10 seconds. Experiments with stimuli of lighter weight, such as the common pin, revealed these changes to an even more striking degree. A summary of the observations are recorded in table 2.

TABLE 2.—*Application of Weight of Common Pin, with Point, Separately on Dorsum of Each Index Finger at Distal Phalanx.**

Right		Left	
Time, Sec.	Sensation	Time, Sec.	Sensation
1	Pinpoint	1	Pinpoint
20	Pinpoint	10	Pinpoint
30	Pinpoint	14	Fluctuation in sensation
40	Pinpoint and pain	19	Pressure
55	Pressure and pain	29	Less pressure
70	Pressure and pain	45	Pressure sensation almost gone
80	Dull pressure; no pain	55	No sensation
95	Dull pressure; no pain	63	Stimulus removed and sensation of "pin" returned
105	"Pin," pain and pressure	78	After-sensation gone
120	"Pin" and pressure		
135	Sensation still there but diminishing		
150	Tingling sensation		
165	Stimulus removed; after-sensation of "pin" and tingling continued for the next three minutes, even though patient saw that there was no pain-inducing stimulus there; after-sensation fluctuated to a great extent		

* The pin was applied and allowed to rest on the skin, being held in place by a small ring stand. The patient felt the prick of the pin as soon as it came in contact with the skin. The stimulus was applied first to one hand and after a 5 minute interval, to the other.

Simultaneous applications of 5 Gm. weights at the base of the great toe yielded sensations which were about equal on the two sides. The patient perceived a sharp pain bilaterally, which was most acute on the right side. On the right the adaptation time seemed to be prolonged, as was the after-sensation. Table 3 is a summary of observations with application of a 2 Gm. weight.

Simultaneous application of a 2.5 Gm. weight stimulus on the right side and of a 5 Gm. weight stimulus on the left (each at the base of the great toe) produced a sensation of dulness (no point) on the right and of a sharp point on the left.

On removal of the stimulus, at the end of 60 seconds, an after-sensation of a point on the right side was reported, which lasted over 45 seconds. There was no after-sensation on the left side. Repetition of this experiment later produced pain bilaterally, which lasted only 5 seconds on the right side. When a much stronger stimulus (15 Gm.) was applied on the left side and 2.5 Gm. was applied on the right side, he had no sensation on the right during the simultaneous application of stimuli but experienced a definite after-sensation on the right when both stimuli were removed. Thus, the patient showed the phenomena of decreased adaptation time and of cutaneous extinction during bilateral simultaneous but unequal stimulation.

Various parts of the body were tested in this manner, but the most profound disorders in after-sensation and adaptation time were present in the right hand and foot, particularly in the distal portions.

TABLE 3.—*Application of 2 Gm. Weight with No. 10 Needle to Base of Fifth Toe, Dorsal Side, Separately on Right and Later on Left Side*

Left		Right	
Time, Sec.	Sensation	Time, Sec.	Sensation
	"Pin" felt as soon as applied		"Pin" felt as soon as applied
11	Pain getting duller	10	Pinpoint sensation weaker
19	Pinpoint sensation fluctuating	18	"Pin" barely felt
27	Pinpoint sensation weak and almost all gone	29	Pinpoint felt
40	Pinpoint and pressure felt	42	Pressure felt
50	Pinpoint and pressure sensation	50	Faint pressure sensation
60	Patient not certain whether pinpoint is there	60	Patient not sure stimulus is there
72	Stimulus removed but pinpoint still felt	80	No sensation
90	Sensation gradually growing		
100, 120, 150	After-sensation weaker during next few minutes, but sensation of point fluctuates		
180	After-sensation still present		
210			
235	All after-sensation gone		

At the conclusion of all these experiments, the patient volunteered the information that the sensation on the right side seemed more painful and lasted much longer than that on the left side. Subsequent repetition of these experiments in the fingers and toes yielded similar results. However, the patient observed that although the pain on the right side always lasted longer, it not infrequently seemed duller than, or not so sharp as, that on the left side; also, it was found that at times the pain sensation seemed to disappear earlier than that on the left.

At no time was the pain sensation disagreeable, nor did it ever have the characteristics of thalamic pain.

2. Temperature Sensation: (*a*) When applied separately, a metal object with a temperature of 23 C. felt colder in the left hand than in the right hand. When the patient held one of these metal objects with each hand simultaneously the sensation of coldness gradually diminished and slowly changed to warmth. However, the change in sensation on the right lagged by more than one minute, and as time continued the lag became more pronounced. The object in the right hand felt progressively "colder" than that in the left.

(*b*) The two hands were then placed in a bowl of water (23 C.). The initial sensation in both hands was that of coldness, but in time changes appeared. These are summarized in table 4.

From these observations it is evident that the adaptation time was much longer on the right side than on the left. Because of the gradual and differential nature of the changes the exact duration could not be calculated, but apparently at 68 seconds the left hand began to show a change which was more rapid than that in the right. The difference between the two hands was maintained for the next 140 seconds, when adaptation in the right hand caught up with that in the left. An after-sensation of coldness was apparent in the right hand, and this lasted well over 4 minutes.

(*c*) On holding a cube of ice in each palm, the patient had simultaneous sensations of coldness in the two hands, but that on the left side was more pronounced. In 110 seconds burning pain appeared in both hands, but was more intense in the right hand. In 170 seconds both hands felt equally cold. Of course, there was no manifest adaptation.[15] When the ice was removed from the palms

TABLE 4.—*Simultaneous Immersion of Both Hands in a Bowl of Water (23 C.)*

Time, Sec.	Sensations Reported
10	Both hands feel cold
40	No change
55	No change
68	Left hand is getting warmer; right hand remains colder
95	Left hand feels warmer than right
115	Definite difference in temperature sense; right hand feels colder than left
160	Difference is still present (temperature of water is now 25 C.)
180	Difference is beginning to be less apparent
210	Hands feel of equal warmth
250	No difference in temperature sensation
280	Right hand feels colder than left
315	Right hand feels colder than left and has a "sensation of numbness," or "dead feeling"
410	Right hand still feels colder than left, cutaneous temperatures as measured with dermotherm are equal on the two sides
480	Difference is still present, but now it is not apparent unless patient "concentrates" on it
500	Difference on right persists, but it is less pronounced

at 200 seconds after-sensations of coldness mixed with burning and dull pain were present in both. These after-sensations, which fluctuated in intensity, were of long duration. However, the after-sensations on the right were more prolonged and more vivid than those on the left. The patient exclaimed that he had the sensation of still holding the ice in the right hand, and he could even sense the weight and the wetness. In the left hand he felt a burning pain.

3. Tactile Sensation: This modality showed the same characteristics as those which were found for pain. The adaptation time was often prolonged, and the duration of after-sensation extended from 1 to 3 minutes in the right hand and foot.

The disturbances were most pronounced in the acral portions of the extremities on the right side. Simultaneous application of a hair analogous to von Frey's

15. Adaptation has certain limits. In the normal person, if the hand is held in water which is only a few degrees above or below the temperature of the skin, the sensations of warmth or cold diminish and disappear within a short time. However, if the hand is held in water as low as 10 C., the sensation of cold persists for a long time, and there seems to be no manifest adaptation. With higher temperatures, above 45 C., there is virtually no adaptation, because of injury to tissue.

hairs on each side at corresponding foci produced a sensation of touch bilaterally, but more acute on the right. Adaptation was much quicker on the left. A prolonged after-sensation was found on the right but not on the left.

Simultaneous application of a strong tactile or painful stimulus on the left and a tactile stimulus to the corresponding focus on the right side produced no sensation on the right side, but only on the left. Thus, the patient manifested the phenomenon of cutaneous extinction during double simultaneous, but unequal, stimulation. However, on the removal of both stimuli there occurred an after-sensation on the right, which seemed to be more apparent and longer in duration than the one on the left.

4. Other Perceptions: (*a*) Vibration sense was about equal on the two sides. He felt the vibrations in the right finger for 30 seconds (the examiner felt the same vibration for 35 seconds) and in the left finger for 37 seconds (examiner felt the same vibration for 34 seconds). In the great toe, vibration was felt for 15 seconds on the right and for 19 seconds on the left. On the removal of the tuning fork, the patient had a prolonged after-sensation of touch but not of vibration in the tested areas of the right extremities. There was no noticeable after-sensation on the left; at least it did not last long.

(*b*) Appreciation of passive movement and ability to recognize position of the digit or toe in space were normal in all respects.

(*c*) Two point discrimination was excellently performed on the two sides. He could differentiate two points when 3 mm. apart (on the right side as well as on the left). Here, again, he complained of an after-sensation of a point on the right side when the compass was removed.

(*d*) Point localization was normal. He could localize correctly every stimulus applied to different parts of his body.

(*e*) Stereognosis was intact. He could recognize various objects placed either in his right or in his left hand. He was able to describe texture, shape, size and other sensations evoked by the tested object. Of course, when he held identical objects between the first two fingers of each hand for a long period without moving his digits or hands, the factors of adaptation became apparent, thus leading to a difference between the two sides. The impression of the object on the right became duller and seemed to become adapted more quickly than that on the left.

(*f*) Barognosis was normal. He could recognize small differences in weights and compare them with either or both hands. During these tests it was noted, however, that the patient had a prolonged after-sensation of a weight in the right hand. A 480 Gm. weight held for 3 minutes with the left hand produced an after-sensation of weight for 10 seconds, whereas the same test with the right hand left an after-sensation for 2 minutes. Equal weights placed simultaneously in the two hands for 3 minutes produced a sensation of heaviness in the right hand throughout and after the test. The after-sensation in the right hand lasted over 3 minutes. Beyond this period there seemed to be a fluctuation of sensation, during which the patient reported an alternating "heaviness" and "lightness" in the hand.

(*g*) Graphesthesia was normal with single or double simultaneous stimulation. The figure writing, however, produced a noticeable after-sensation in the extremities on the right side.

Comment.—The outstanding features in this case are (*a*) prolongation of after-sensations; (*b*) delay in sensory adaptation, and (*c*) appearance of a dull ache during the application of continuous stimulus, pain or

pressure. The last symptom (*c*) might have been responsible for the apparent prolongation of the adaptation time for pain sensation. The dull ache and the occasional burning and tingling which appeared on continuous stimulation were somewhat similar to the hyperpathia which is found with lesions of the thalamus. However, there were no other clinical signs of such involvement. Interestingly enough, with double simultaneous and equal stimulation the sensation in the affected limbs seemed to him to be keener than that felt on single stimulation. This enhancement of a sensation with paired stimulation seems to be the converse of the phenomenon of extinction, which could be elicited in some cases under the same conditions. In fact, in this patient the simultaneous application of a strong stimulus on the normal side and a weak stimulus on the affected side produced a reduction in sensitivity, and even a reduction in sensory adaptation time, in the affected limb. Thus, this patient showed both phenomena, namely, (*a*) enhancement of a sensation with apparent prolongation of the adaptation period and (*b*) reduction of the adaptation period with ultimate extinction of sensation. It is not improbable that these phenomena are related and appear to be the positive and the negative phase of the various sensory mechanisms which are operative in this patient. Analogous to these positive and negative phases of a given sensory mechanism are the facilitation and suppression (or extinction) phenomena for motor function, as demonstrated by Dusser de Barenne and his collaborators.[16] They found that by changing the strength, frequency, duration, character and timing of stimuli, either facilitation or extinction could be obtained on exciting a given focus in the motor cortex of the chimpanzee or monkey. Similar positive ("firing") and negative ("suppression") changes were found on stimulating the sensory cortex.[17] These experimental data may conceivably explain the clinical observation made in patients with injuries of the parietal lobe, the stimuli in these cases arising, of course, from cutaneous zones.

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16. (*a*) Dusser de Barenne, J. G.: Simultaneous Facilitation and Extinction of Motor Response to Stimulation of a Single Cortical Focus, Am. J. Physiol. **116**:39-40, 1936. (*b*) McCulloch, W. S.: On the Nature and Distribution of Factors for Facilitation and Extinction in the Central Nervous System, ibid. **119**: 363-364, 1937. (*c*) Dusser de Barenne, J. G., and McCulloch, W. S.: Factors for Facilitation and Extinction in the Central Nervous System, J. Neurophysiol. **2**:319-355, 1939. (*d*) Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: The Motor Cortex of the Chimpanzee, ibid. **4**:287-303, 1941.

17. Dusser de Barenne, J. G., and McCulloch, W. S.: Functional Organization in the Sensory Cortex of the Monkey (Macaca Mulatta), J. Neurophysiol. **1**:69-85, 1938. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Functional Organization of Sensory and Adjacent Cortex of the Monkey, ibid. **4**:324-330, 1941.

Another feature which this, and the first, case illustrates is that a stimulus applied on one side of the body alters the sensation obtained on the opposite side or in other parts of the body.[18] All these observations support the experimental observations of Dusser de Barenne, who concluded that sensory function is bilaterally represented.[19] One sensory cortex receives impulses from both sides of the body; conversely, a sensation on one side of the body is represented in both sensory cortices.

GENERAL COMMENT

It is well known that many forms of sensation are adaptable. Adaptation for pressure has been recognized for years. For example, a glove on the hand, a ring on the finger or hat on the head become unfelt after a short interval. Adaptation for thermal, olfactory and gustatory sensations has been described.[20]

Adaptation for pain has also been recognized, and, notwithstanding doubts expressed by Boring,[20b] Strauss and Uhlmann[21] (1919) and, later, Burns and Dallenbach (1933)[22] found that pain is adaptable. The adaptation times, however, vary considerably with the subject and with the spot stimulated. There are individual differences and wide fluctuations. The period of adaptation is not greatly influenced by the intensity of the stimulus, by fatigue or by ennui. Slight movements of the stimulus or of the tissue beneath the stimulus do not interfere with the phenomenon of adaptation. All that seems to be required to obtain the phenomenon is a stimulus of unvarying intensity. The pain aroused by a punctiform stimulus is replaced by a sensation

18. There are instances in which a stimulus applied to an anesthetic side of the body elicits a sensation on the opposite (normal) side (Ray, B. S., and Wolff, H. G.: Studies on Pain: "Spread of Pain"; Evidence on Site of Spread Within the Neuraxis of Effects of Painful Stimulation, Arch. Neurol. & Psychiat. **53**: 257-261 [April] 1945). This has been found in patients with a lesion of the spinal cord produced by ventrolateral chordotomy. Ray and Wolff explained the perception of pain on the normal side when a strong noxious stimulus is applied to the analgesic area on the basis of spread of excitation via internuncial neurons in the spinal cord. This "postulated spread of excitatory processes associated with pain of high intensity primarily involves the segmented structures, although secondarily the suprasegmental structures are implicated in perception, localization and reaction."

19. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, A. Research Nerv. & Ment. Dis., Proc. **15**:274-278, 1935.

20. (*a*) Woodworth, R. S.: Experimental Psychology, New York, Henry Holt & Company, Inc., 1938. (*b*) Boring, E.: Sensation and Perception in the History of Experimental Psychology, New York, D. Appleton-Century Company, Inc., 1942.

21. Strauss, H. H., and Uhlmann, R. F.: Adaptation to Superficial Pain, Am. J. Psychol. **30**:422-424, 1919.

22. Burns, M., and Dallenbach, K. M.: The Adaptation of Cutaneous Pain, Am. J. Psychol. **45**:111-117, 1933.

of pressure before adaptation takes place. Thus, there is a gradual subsidence from maximal pain, evoked by a given stimulus (2.5 to 7.5 Gm.), through a sensation of pressure to total indifference. The sequence of experiences reported by a subject who has a 2.5 to 7.5 Gm. weight stimulus with a no. 10 needle point applied to the forearm is as follows: sharp, intense pain; sharp pain; pain; dull pain; weak pain; pressure; weak pressure; tickle; no sensation. The adaptation time varies in different parts of the body, but it seems to be approximately equal for corresponding points on the two sides.[23] On removal of the stimulus, there is usually an after-sensation.

Thus, in the normal subject, if it takes 80 seconds for sensation produced by a 2.5 Gm. weight point stimulus to disappear on the right index finger, it might take 70 to 90 seconds on the left index finger. However, if the total adaptation time is 10 or 15 seconds on one side and 70 to 90 seconds on the other, the difference becomes significant. It is noteworthy that the reduction in the entire adaptation period is not always proportional for each of the intrinsic changes in sensation experienced in various pathologic conditions. For instance, in a defective sensory area due to a cerebral lesion the total adaptation time for a 5 Gm. stimulus may be 15 seconds. Here, the sensation of pain may change to one of pressure at the end of 10 seconds, there remaining a sensation of pressure for 5 seconds. On the other hand, the adaptation time in a sensory area affected by a lesion of a peripheral nerve may be 50 seconds, and here the sensation of pain might disappear in 10 or 15 seconds, leaving a sensation of pressure for 40 or 35 seconds.

In summary, sensory adaptation in cases of cerebral lesions is represented by changes from pain to pressure which take place much more rapidly than in cases of lesions of the peripheral nerves. The total time required for adaptation is usually shorter in cases of lesions of the parietal lobe than in cases of lesions of peripheral nerves. As a rule, the sensation of pressure, which follows the initial sensation of pain, during adaptation, is of longer duration with peripheral than with central lesions. Adaptation for such perceptual performances as stereognosis, barognosis and kinesthesia, with resultant alteration in the body image, probably exists in the normal person, but few, if any, studies of such a phenomenon have been made by the neurologist or the psychologist. The first case here presented demonstrates the presence of such a mechanism for some of these perceptions. The disappearance of a complex perception, such as the position or presence of a limb in space or the ability to sense a weight during a prolonged act, would seem to point to "adaptation" on a central or cortical

23. Some of the studies on pain adaptation in the normal subject in this series have been made by Lieut. Comdr. L. D. Boshes (MC), U.S.N.R.

level, despite the fact that the primary modalities are also affected in these tests. Certainly, "adaptation" for barognosis and other complex cutaneous perceptions must ultimately occur in the parietal cortex. Thus, lesions in the cortex may lead to a reduction in the sensory adaptation time. Interference with sensory conduction in the periphery may also decrease the time, but not nearly as much as that caused by a cortical lesion. It is not unlikely that central adaptation occurs also in visual perception [24] and should be apparent under pathologic conditions. As a matter of fact, in a series of patients with visual disturbances produced by gunshot wounds implicating the optic pathways, certain observations seem to indicate that the mechanism for central adaptation may be operating for visual perception. Thus, in a case of a gunshot wound through the midparieto-occipital area, the patient found that if he fixed on a point for a few seconds three quarters of the entire field of vision "faded out." Perimetric examination revealed apparently intact fields for perception of motion, but transient defects for color, in these three quadrants. Since in this patient no visual stimuli were added to his field of vision and since fixation was steady, it would be difficult to explain the "fading out" of his perception in terms of the phenomenon of visual extinction alone.[25] A possible interpretation is that the vision "faded out" on the basis of central adaptation.

Although most patients with injuries to the parietal lobe show a decrease in the period of adaptation, there are some instances, such as case 2, in which the period is prolonged. This prolongation may be only apparent, since it seems to be associated with a fluctuating dull, sometimes tingling, pain, which has been found to occur late in the period of continuous application of a stimulus. This dull pain may thus interfere with the patient's ability to adapt to pain, temperature and pressure sensations. Yet it is uncertain which comes first—whether the appearance of pain prevents completion of adaptation or prolongation of the adaptation causes the appearance of pain. Since there is no initial alteration of the threshold and no hyperpathia in these cases, it would seem that the latent dull pain is due to lack of adaptation, and perhaps a resultant summation. A possibility which must be considered is that a stimulus in the parietal cortex

24. In point of fact, peripheral mechanisms of adaptation in vision (dark and light adaptation) have been thoroughly studied by physiologists and psychologists.

25. It should be recalled that extinction of visual perception (as well as cutaneous perception) occurs on double simultaneous stimulation. The patient can perceive a stimulus placed in the affected field of vision, but as soon as another stimulus is placed in the normal field perception in the affected field becomes extinct. He cannot perceive simultaneously objects placed in the normal and in the involved area.

may "fire" neurons in the thalamus and thus indirectly produce thalamic pain.[26] Whatever the explanation may be, it is a fact that in a patient with injury to the anterior parietal lobe the sensory adaptation period seems to be prolonged.

Concomitant with a pathologic increase in adaptation time is a prolongation of the after-sensation. Painful, thermal or tactile sensations may persist after the removal of the respective stimulus or, having been lost under adaptation, may recur on the withdrawal of the stimulus.[27] In most cases of injury to the parietal lobe, in which, as has been seen, adaptation time is reduced, the duration of the after-sensation is likewise reduced or abolished. The same is true in cases of injury to peripheral nerves. Conversely, prolongation of after-sensation is found but uncommonly in cases of damage to the parietal lobe. In cases of injury to peripheral nerves the after-sensation is not infrequently prolonged, especially in the hyperesthetic cutaneous area.

This prolongation of cutaneous after-sensation[28] is also difficult to explain. In the normal subject after-sensations may show instability and variability, which are dependent on central factors. According to Holland,[29] it makes a great difference whether the subject is passive or whether he assumes an active attitude, in which he attempts to secure as much cutaneous experience as possible. For a given stimulus during a passive attitude, the after-sensation lasted from 0.7 to 2.0 seconds, and the secondary after-sensations were few and brief. During an active attitude, the primary after-sensations lasted an average of 4 seconds (although sometimes as long as 200 seconds), and the secondary after-sensations were numerous and often of long duration. Although an active attitude may thus produce persistence of an after-sensation in the normal subject, it could not explain the phenomenon in case 2, in which after-sensations were prolonged on the affected side, particularly in the distal portions of the extremities. One must assume that the persistence of the after-sensation was due to centrally excited sensations as result of a lesion in the anterior parietal lobe.

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26. Dusser de Barenne, J. G.: Sensorimotor Cortex and Thalamus Opticus, Am. J. Physiol. **119**:263, 1937. Dusser de Barenne, J. G., and McCulloch, W. S.: The Direct Functional Interrelation of Sensory Cortex and Optic Thalamus, J. Neurophysiol. **1**:176-186, 1938.

27. The experimental psychologist divides after-sensations into two phases: persistence, or primary after-sensation, and recurrence, or secondary after-sensation.[20b]

28. An analogous situation may be found in visual after-imagery. In a patient with a lesion of the visual pathways and cortex there was marked prolongation in the duration of the visual after-image.

29. Holland, R. T.: On the After-Sensation of Pressure, J. Exper. Psychol. **3**:302-318, 1920.

These observations suggest that perception is greatly influenced by the mechanisms of sensory adaptation and after-sensation, which are partly of central origin. With disease these mechanisms become apparent, sometimes to such an extent that they produce manifest symptoms.

Whether adaptation taken in a clinical sense (as used in this paper) is directly related to the phenomena of adaptation in the psychologic sense (as measured at the peripheral level) is difficult to say. It is tempting to draw an analogy between the clinical adaptation phenomenon for perceptions and the phenomenon of adaptation of sensory function as described by physiologists, such as that for single optic nerve fibers, described by Hartline [30] and others. At least it is reasonable to assume that these characteristics of function (changes in adaptation) at the peripheral end organ and neuron are reflected in the more complex functions of the cerebral cortex. It may also be argued that central adaptation is the result of cumulative effects of adaptation in single neuronal units (in the physiologic sense). But in view of the paucity of available data at this time such deductions are still in the speculative stage.

SUMMARY

A patient with a gunshot wound of the left posterior parietal and occipital lobes showed disturbances in visual, cutaneous and proprioceptive senses on the right side of his body. These defects were elicited under special conditions. Whereas with single stimulation his vision appeared to be intact, simultaneous stimulation of his right and left fields of vision caused the image on his right to become extinct. This phenomenon of extinction was found in various forms, from fluctuation and blurring to complete invisibility of an image. A similar phenomenon was found for cutaneous perception. Besides this, the patient showed a reduction in the adaptation time for cutaneous and proprioceptive modalities. The latter was pronounced enough to produce a disorder in his body image.

Another patient, with a gunshot wound in the left anterior parietal and posterior frontal lobes, showed motor and sensory disturbances in the right side of his body. The sensory changes could be elicited only under special conditions and were expressed as a prolongation of the periods of sensory adaptation and after-sensation. With paired equal stimulation, sensation was apparently enhanced on the affected side. With paired simultaneous stimulation in which a strong stimulus was applied to the left side and a weak stimulus to the right side,

30. Hartline, H.: Response of Single Optic Nerve Fibers of Vertebrate Eye to Illumination of Retina, Am. J. Physiol. **121**:400-415 (Feb.) 1938.

there was reduction of sensory adaptation time, and even extinction of sensation. This case thus illustrates the phenomena of "enhancement and extinction" of sensation, either of which could be obtained on stimulating the same area of the skin at different times and under different conditions. It is analogous to the experimental observations made by Dusser de Barenne and associates [16d] for motor function in the chimpanzee. These patients also showed decrease or increase in after-sensations.

These observations reveal that most of the disturbances in these patients were due to normal mechanisms (such as rivalry with resultant dominance, sensory adaptation and after-sensations) which became apparent under pathologic conditions, such as lesions in the parietal lobe. Why these mechanisms become so apparent is not clear. Without the foregoing considerations and special investigations of sensations, most of the symptoms could not be explained, because routine neurologic examination for sensation revealed an essentially normal status in both these patients.

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SIGNIFICANCE OF CORNEAL AND PHARYNGEAL REFLEXES IN NEUROLOGY AND PSYCHIATRY

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DURING the course of the neurologic examination, deviations from classic normality occur even in the absence of organic disease of the nervous system. Much experience and intuition are required to distinguish normal variations from pathologic signs, and too frequently the presence of asymmetry is allowed to constitute the determining factor. It would seem only reasonable to assume that some of the determinants of these deviant, but nonpathologic, signs might have significance for the clinician. For example, variations in reflex responses might be found to occur in definite patterns, so that a single observation could be interpreted in terms of its conformity to the pattern set by the other reflexes rather than in terms of an absolute standard. Another possibility is that psychic attitude might be expressed by, or might determine, patterns of reflex variability. Accordingly, complete neurologic examinations were performed and the results recorded in conjunction with diagnostic psychiatric interviews for a series of patients, and relationships are being sought in this codified material. In this paper the distribution of variations in corneal and pharyngeal reflexes and their relations to other physical and to mental signs are presented.

It is current medical belief, expressed less frequently in psychiatric textbooks than in others, that hysterical conversion symptoms are often accompanied by absence of corneal and pharyngeal reflexes. Monrad-Krohn [1] stated that "the pharyngeal reflex may be absent in hysteria," thus implying that in the absence of hysteria (and of organic disease of the brain) this reflex is always present. Moreover, he went on to say that, although the "conjunctival reflex is often absent in normal individuals, the corneal reflex is a constant phenomenon, the absence of which has pathologic significance." Wechsler [2] and Brain,[3] on the

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1. Monrad-Krohn, G. H.: Clinical Examination of the Nervous System, ed. 7, New York, Paul B. Hoeber, Inc., 1941.

other hand, unequivocally stated that the corneal, as well as the pharyngeal, response may be absent in hysteria. In view of this popularly established belief, the results of actual analysis have proved surprising.

MATERIALS AND METHOD

One hundred and forty-one patients were included in this study. Of these, 58 were taken from the wartime population of St. Elizabeths Hospital, and the group consisted primarily of young Navy men in the various stages of their acute psychoses; the remaining 83, a group composed for the most part of young criminal psychopaths and maladjusted persons, whose mental state falls frequently just within the limits of psychiatric normalcy, were examined at the Medical Center for Federal Prisoners. Of the entire group, the diagnosis of encephalopathy was made for 30 patients. The degree of involvement was usually mild or moderate, and the chief etiologic factors were syphilis of the central nervous system, arteriosclerosis, alcoholism and trauma. These 30 patients are referred to later as the "organic group," which by our definition excludes 8 patients who exhibited convulsive seizures but no neurologic abnormality other than a dysrhythmic electroencephalogram.

It is thought advisable to describe in some detail the technics employed for the elicitation of the various reflexes studied. Reflex response to tactile stimulation of the cornea was tested in the following manner: A small wisp of sterilized absorbent cotton was drawn out and twisted to form a thick and slightly tapering thread at least 1 inch (2.54 cm.) long. Care was exercised to see that the thread terminated abruptly at the stimulating end. The patient was instructed to look upward and to the right. The cotton thread was then slowly advanced close to, and parallel with, the surface of the face and the conjunctiva of the left eye from left to to right until its free end rested securely on the left cornea, infralateral to the pupil and at a point about 2 mm. inside the sclerocorneal junction (limbus corneae). Thus, the cotton stimulator and the moving hand of the examiner were at all times outside the patient's field of vision. An analogous procedure was performed on the right cornea. Responses were graded on the basis of promptness and forcefulness into five categories: normal; slightly, moderately and greatly diminished, and absent. The chief purpose of such fine grouping was to insure careful observation. For statistical analysis, however, the first three categories were combined to form the positive corneal (C+) group, and the last two, to constitute the negative corneal (C—) group.

The following procedure was used to test the pharyngeal reflex: The patient was approached with a flashlight and a tongue depressor. He was instructed to open his mouth, and as the tongue depressor was advanced he was requested to say "Ah," just as though an ordinary inspection of the pharynx were proceeding. The stick was gently passed backward under plain view until it rested securely against the posterior pharyngeal wall in the midline. Responses varied from prompt and forceful gagging and coughing movements to none at all. Intermediate responses consisted of orderly contractions of the faucial musculature. As with the corneal reflexes, responses were classified under five groups, from which two

2. Wechsler, I. S.: Textbook of Clinical Neurology, ed. 4, Philadelphia, W. B. Saunders Company, 1939.

3. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940.

compound categories, positive pharyngeal (P+) and negative pharyngeal (P—) reflexes, were formed for purposes of statistical comparison.

Other examinations and tests, including the Mayer test and tests for the abdominal (skin), deep and Hoffmann reflexes, were executed by standard manipulations, and conventional criteria were followed.[4]

RESULTS

1. *Distribution of Reflex Responses in Entire Series.*—It will be observed (table 1) that over one third of all the patients in this series exhibited a marked diminution or entire absence of the corneal reflex (C—), and that this proportion is scarcely decreased when the patients with organic disease are removed from the series. Of the latter group, more than half showed absence of the corneal reflex. (In only 1 patient was there any significant difference between the responses on the two sides.) With respect to the pharyngeal reflexes, more than two thirds of the entire series fell in the negative group, and when the patients with organic disease are excluded, almost three quarters of the patients showed the marked diminution or absence of response. Moreover, a positive pharyngeal reflex was twice as frequent among the patients with organic disease as among the others, and this difference is significant at the 1.6 per cent level (odds, 60:1).

The results obtained by combining the corneal and the pharyngeal categories to form four groups (C+ P+, C+ P—, C— P+ and C— P—) are also included in table 1. It appears, first, that there is no significant correlation between the corneal and the pharyngeal responses in patients either of the nonorganic or of the organic group. Second, the distributions for the total series and for the patients without organic disease are remarkable in that in each series almost half the patients fall into the C+ P— group, about one-quarter each in the C+ P+ and in the C— P— group, and the small remainder in the C— P+ group. This must not be interpreted as indicating that there is any physiologic antagonism between a negative corneal reflex and a positive pharyngeal reflex, for when the incidence of negative corneal reflexes (C—), 36 per cent, is multiplied by the incidence of positive pharyngeal reflexes (P+), 31 per cent, in the total series, the product is 10 per cent, which is approximately the observed incidence for the C— P+ group. Among the patients with organic disease, however, the results are different. It will be recalled that here one-half the patients exhibited a positive corneal reflex and one-half exhibited a positive pharyngeal reflex. Assuming that the independence of corneal and pharyngeal responses holds even among the patients with organic disease, one may expect that about

4. Monrad-Krohn.[1] Wechsler.[2] Brain.[3]

TABLE 1.—*Distribution of Patients According to Corneal and Pharyngeal Responses*

	1 Sum or Mean	2 C+	3 C−	4 P+	5 P−	6 C+ P+	7 C+ P−	8 C− P+	9 C− P−
A. Total series	141	90	51	44	97	31	59	13	38
B. Percentage of total series	100	64	36	31	69	22	42	9	27
C. Patients without organic disease	111	76	35	29	82	23	53	6	29
D. Percentage of patients without organic disease	100	68	32	26	74	21	48	5	26
E. Patients with organic disease	30	14	16	15	15	8	6	7	9
F. Percentage of patients with organic disease	100	47	53	50	50	27	20	23	30
G. Percentage of patients with organic disease in total series	21	16	31	34	15	26	10	54	24

one quarter of the patients will fall into each of the four groups; and they do. This difference between the distribution of the patients with organic disease and that of the total population among the various CP groups is so great that the odds are much less than 1 : 1,000 that any randomly selected group similarly analyzed would differ more from our total series ($X^2 = 34.75$).

Another way of presenting the same results is to compute the proportion of patients with organic disease within any of the established categories. Thus, as expected, while only 16 per cent of the patients with positive corneal responses belong to the organic group, 31 per cent of the patients with negative corneal responses belong to that group, whereas 15 per cent of the patients with negative pharyngeal responses and 34 per cent of those with positive pharyngeal responses belong to the organic group. In the compound categories, only about 1 of 10 patients in the C + P — category had organic disease of the brain, but more than half the patients in the C — P + classification were considered to have organic disease, and this difference is statistically significant (C. R. = 3).

From these results, it is believed one is justified in stating that any patient who exhibits absence of corneal reflexes in the presence of an active pharyngeal reflex should be strongly suspected of having organic disease of the brain.

2. *Distribution of Reflex Responses According to Diagnostic Groups.* —For the 141 patients in our series, 184 diagnoses were made; the distribution of those diagnoses according to reflex responses is shown in table 2. The percentages given in lines D, H and J were constructed by dividing the number of diagnoses for the groups with schizophrenia, psychopathic personality and organic disease of the brain, respectively, by the number of patients in the column. Thus, the entry 39 per cent in line D, column 2, signifies that 39 per cent of the patients in the group with positive corneal responses (C +) bore the diagnosis of schizophrenia. Except in the group with organic disease, which has previously been discussed, dramatic differences do not appear. The differences between the incidence of psychopathic personality in the groups with positive and negative corneal reflexes (C + and C —), on the one hand, and the incidence of schizophrenia in the groups with positive and negative pharyngeal reflexes (P + and P —), on the other, are less than 1.5 times their respective standard deviations, and do not even reach the 10 per cent level of significance.

However, of the 56 schizophrenic patients, 17 had at the time of examination recovered practically completely, 10 were slightly ill, 18 were moderately so and only 11 were considered seriously ill. By assigning values of 0, 100, 200 and 300 to these four groups, respec-

TABLE 2.—*Distribution of Patients According to Diagnosis and Corneal and Pharyngeal Responses*

	1 Total	2 C+	3 C−	4 P+	5 P−	6 C+ P+	7 C+ P−	8 C− P+	9 C− P−
A. Total number of patients	141	90	51	44	97	31	59	13	38
B. Total number of diagnoses	184	118	66	60	124	42	76	18	48
C. Number of schizophrenic patients	56	35	21	14	42	11	24	3	18
D. Percentage of schizophrenic patients (C/A)	40	39	41	32	43	35	41	23	47
E. Index of illness* among schizophrenic patients	141	160	110	107	152	118	179	67	117
F. Amount of schizophrenic activity* for group (D×E=C×E/A)	56	63	45	34	65	41	73	15	55
G. Number of patients with psychopathic personality	49	35	14	15	34	11	24	4	10
H. Percentage of psychopathic patients (G/A)	35	39	27	34	35	35	41	31	26
I. Number of patients with organic disease of brain	30	14	16	15	15	8	6	7	9
J. Percentage of patients with organic disease of brain (I/A)	21	16	31	34	15	26	10	54	24
K. Number of patients with simple adult maladjustment	17	11	6	8	9	6	5	2	4
L. Number of mentally defective persons	10	9	1	4	6	3	6	1	..
M. Number of epileptic patients †	8	7	1	2	6	2	5	..	1
N. Number of psychoneurotic patients	6	4	2	..	6	..	4	..	2
O. Number of patients with manic-depressive psychosis	5	1	4	1	4	..	1	1	3
P. Miscellaneous groups	3	2	1	1	2	1	1	..	1

* The indexes in line E were computed by averaging assigned values of 0, 100, 200 and 300 for recovered and slightly, moderately and very ill schizophrenic patients, respectively. The figures in the following line, F, were obtained by multiplying the appropriate figures in lines D and E, so that the products measured the net amounts of schizophrenic activity for the respective groups.

† Includes patients exhibiting seizures without clinical evidence of encephalopathy.

tively, index numbers were obtained which vary among the several CP categories, as indicated on line E of table 2. For example, 160 (line E, column 2) indicates that the severity of the psychotic process among the schizophrenic patients with positive corneal reflexes was on the average between slight and moderate. Now, by multiplying this average degree of activity among the schizophrenic patients by the percentage incidence of schizophrenia, one obtains an index which can be said to measure the average schizophrenic activity for the column (line F). Thus, the average schizophrenic activity among the patients with negative pharyngeal reflexes is 65, and that among the patients with positive pharyngeal reflexes, 34, with a difference of 31, which is significant to the 5 per cent level (C. R. = 1.91). The analogous computation for positive and negative corneal reflexes yields a difference of 18, which is not significant.

It appears from the foregoing analysis that the schizophrenic process may be associated with obtundation of the pharyngeal reflex.

3. *Relation of the Corneal and Pharyngeal Reflexes to the Abdominal Reflex.*—In table 3 the results of examination of the abdominal reflexes are summarized. Three groups of patients are considered: those with normal abdominal reflexes, those with overactive reflexes and those with underactive reflexes, the last group including patients with absence of reflexes. In addition, index numbers for average activity of the abdominal reflex were computed by assigning a value of 0 to patients with normal reflexes, 100 to patients with overactive reflexes, —100 to patients with underactive reflexes and —200 to patients with absence of reflexes. (When the abdominal reflexes were asymmetric, the patient was classified with respect to the more abnormal reflex.) In lines D and K, these index numbers are listed for the corneal and pharyngeal categories. The contrast between the mean index for patients with organic disease (—74) and the mean index for patients with nonorganic disease (—3) is striking and is certainly consistent with the well established underactivity of the abdominal reflexes in patients with organic disease of the brain.

Closer examination of line D reveals that division of the patients into categories of positive and negative corneal reflexes (C + and C —) yields groups whose average abdominal reflex activity does not differ from the normal. However, a similar classification in terms of positive and negative pharyngeal reflexes results in a significant difference (C. R. = 4); patients with an active pharyngeal reflex exhibit, on the average, a slightly overactive abdominal response, while patients with an inactive pharyngeal reflex tend to exhibit a slightly underactive abdominal reflex. According to some opinions expressed in the litera-

TABLE 3.—*Distribution of Patients According to Abdominal Reflex Activity and Corneal and Pharyngeal Responses*

	1 Sum or Mean	2 C+	3 C−	4 P+	5 P−	6 C+ P+	7 C+ P−	8 C− P+	9 C− P−
A. Total number of patients	86	59	27	31	55	22	37	9	18
B. Total number of patients without organic disease	59	46	13	17	42	15	31	2	11
C. Total number of patients with organic disease	27	13	14	14	13	7	6	7	7
D. Index number for patients without organic disease *	−3	−2	−8	29	−17	27	−16	50	−18
E. Number with normal abdominal reflexes	19	17	2	7	12	6	11	1	1
F. Percentage with normal abdominal reflexes (E/B)	32	37	15	41	29	40	36	50	9
G. Number with overactive abdominal reflexes	20	15	5	8	12	7	8	1	4
H. Percentage with overactive abdominal reflexes (G/B)	34	33	38	47	29	47	26	50	36
I. Number with underactive abdominal reflexes †	20	14	6	2	18	2	12	..	6
J. Percentage with underactive abdominal reflexes (I/B)	34	30	46	12	43	13	39	..	55
K. Index number for patients with organic disease *	−74	−92	−57	−93	−54	−128	−50	−57	−57
L. Number with normal abdominal reflexes	5	3	2	2	3	1	2	1	1
M. Number with overactive abdominal reflexes	3	1	2	1	2	..	1	1	1
N. Number with underactive abdominal reflexes †	19	9	10	11	8	6	3	5	5
O. Percentage of patients with organic disease among those with overactive abdominal reflexes (M/G+M)	13	6	29	11	14	..	11	50	20
P. Percentage of patients with organic disease among those with normal abdominal reflexes (L/E+L)	21	15	50	22	20	14	15	50	50
Q. Percentage of patients with organic disease among those with underactive abdominal reflexes (N/I+N)	49	39	63	85	31	75	20	100	46
R. Percentage of patients with organic disease among total number of patients (C/A)	31	22	52	45	24	32	16	78	39

* Computed by assigning values of 100 to patients with overactive abdominal reflexes; 0 to patients with normally active abdominal reflexes; −100 to patients with underactive abdominal reflexes, and −200 to patients with absence of abdominal reflexes. When unequal abdominal responses were elicited, the patient was categorized according to the more abnormal response.

† Patients with absence of abdominal reflexes included in this group.

ture (cited by Wartenberg [5]), overactivity of the abdominal reflex is attributed to cortical irritation, just as absence is attributed to a destructive lesion of the pyramidal tract. However, Monrad-Krohn (cited by Brock [6]) suggested that activity of the abdominal reflex is increased by a destructive lesion of the red nucleus; i. e., exaggeration and diminution of the reflex are the results of two entirely different mechanisms. Further examination of table 3 will show that among our patients without organic disease of the brain 47 per cent of those with an active pharyngeal reflex had an overactive abdominal response, whereas 29 per cent of the patients with an inactive pharyngeal reflex showed an overactive abdominal reflex. Moreover, the corresponding proportions for patients with an underactive abdominal reflex are 12 and 43 per cent. In short, an overactive abdominal reflex is associated with an active pharyngeal reflex and an underactive abdominal reflex with an inactive pharyngeal reflex; no trace of a dual mechanism appears among these patients.

Reference to column 1, lines O, P and Q, indicates that of the patients with an overactive abdominal reflex, 13 per cent had organic disease of the brain; of those with a normal abdominal reflex, 21 per cent had organic disease of the brain, and of the patients with an underactive abdominal reflex, 49 per cent had organic disease of the brain. These results are entirely consistent with the usual clinical interpretation of absence of the abdominal reflex. From the data given in the foregoing paragraph, one may anticipate a useful and, to our knowledge, hitherto undescribed relationship. If among patients without organic disease of the brain the activity of the pharyngeal and that of the abdominal reflex are closely associated, then the presence of an underactive abdominal reflex or its absence should be a much more reliable indicator of organic disease in the presence of an active pharyngeal reflex than in the presence of an inactive one. In the latter case even patients without organic disease of the brain may be expected to show underactivity of the abdominal reflex. Reference to columns 4 and 5, lines O, P and Q, confirms this a priori conclusion. Thus, among patients with a normal or with an overactive abdominal reflex, the presence or absence of the pharyngeal reflex does not influence the percentage incidence of organic disease of the brain. However, among patients with an underactive abdominal reflex, 85 per cent of those who simultaneously exhibit an active pharyngeal reflex have organic cerebral disease; of those with an inactive pharyngeal reflex, only 31 per cent

5. Wartenberg, R.: Studies in Reflexes: I. History, Physiology, Synthesis and Nomenclature, Arch. Neurol. & Psychiat. **51**:113 (Feb.) 1944.

6. Brock, S.: Anatomical and Physiological Basis of Neurology, Baltimore, William Wood & Company, 1933.

have organic disease of the brain. In this series of patients an underactive abdominal reflex was almost three times as significant of organic disease in the presence of pharyngeal activity as in its absence.

One now has two sets of reflex combinations, each of which is a better indicator of the presence of organic disease of the brain than any of its component reflexes taken individually: first, the combination of active pharyngeal and inactive corneal reflexes; and, second, the combination of active pharyngeal and underactive abdominal reflexes. Although superficially these combinations might seem to be analogous, really they achieve their significance by quite different mechanisms. In the first, in the group with inactive corneal reflex (C —), organic disease is 31/21 times as frequent as in the total population, and in the group with active pharyngeal reflex (P +) it is 34/21 times as frequent. If there is no association between corneal and pharyngeal activity, the frequency for the combination should be 31/21 times 34/21, multiplied by the frequency of organic disease in the general population (21 per cent). This product is 50 per cent, which is almost exactly the frequency observed. The antagonism of the two signs among patients without organic disease of the brain is statistical rather than physiologic. In the second combination, a similar situation prevails but is secondary in importance to a physiologic antagonism between an active pharyngeal reflex and an underactive abdominal reflex in the absence of organic disease of the brain. This second combination is, therefore, a more reliable sign, as the tabulated data readily indicate.

Since an inactive corneal reflex and an underactive abdominal reflex are each more significant of organic disease of the brain than their respective alternatives, it might be expected that the combination of these two responses would show a higher incidence of organic disease than any of the other three possible combinations. The tabulated data are again confirmatory; a regular and orderly decrease in the percentage of organic disease is exhibited with progressive increase in activity of the abdominal reflex and with activity of the corneal reflex, whereas there is no trace of physiologic correlation between the two signs.

4. *Relation of the Corneal and Pharyngeal Reflexes to Mayer's Phalangeal Sign.*—The usefulness of Mayer's phalangeal sign is impaired by the appearance of either underactivity or overactivity in the presence of organic disease of the brain. Monrad-Krohn [1] attributed pathologic significance only to loss of the reflex. Wartenberg [5] conceded that although inactivity is a delicate pyramidal tract sign, the reflex may be absent in normal persons as well. Further difficulty in interpretation is offered by exaggeration of the reflex "with a lesion of the frontomotor region of the brain." Ultimately, then, dependence on asymmetry

TABLE 4.—*Distribution of Patients According to Mayer Reflex Activity and Corneal and Pharyngeal Responses*

	1 Sum or Mean	2 C+	3 C−	4 P+	5 P−	6 C+ P+	7 C+ P−	8 C− P+	9 C− P−
A. Total patient series	74	48	26	23	51	14	34	9	17
B. Total number of patients without organic disease	46	34	12	8	38	6	28	2	10
C. Index of Mayer responses among patients without organic disease	109	112	100	212	87	200	93	250	70
D. Total number of patients with organic disease	28	14	14	15	13	8	6	7	7
E. Index of Mayer responses among patients with organic disease	164	100	228	160	169	75	133	257	200
F. Percentage of patients with organic disease among those with absence of or slight Mayer response	27	28	25	86	15	83	13	100	18
G. Percentage of patients with organic disease among those with moderate or strong Mayer responses	52	32	79	56	47	38	27	75	83
H. Percentage of patients with organic disease among total series of patients	38	29	54	65	25	57	18	78	41

remains; and even here, to quote Wartenberg further, "It may be extremely difficult to say on which side the reflex must be regarded as normal and on which as exaggerated or diminished."

From the data of table 4 inferences appear which may serve as reliable criteria in evaluating the Mayer response. In lines C and E index numbers are given. These indexes are computed by averaging values for 0, 100, 200 and 300 assigned to absence of reflexes and to slightly active, moderately active and extremely active reflexes, respectively. First, it should be noted that the index for 46 patients without organic disease of the brain is 109, while the corresponding index for 28 patients with organic disease of the brain is 164. That is, our patients with organic disease of the brain showed, on the average, a more active Mayer reflex than the patients without organic disease of the brain. (In the computations which appear in the table, the patients whose responses were bilaterally unequal, 9 of the patients without organic disease and 11 of the patients with organic disease, were each classified with respect to the more active of the two reflexes. Classification according to the less active of the two reflexes yields a table with lower indexes but with essentially the same relations.) This difference, which is significant only to the 6 per cent level (C. R.= 1.9), is not an important one but does confirm Wartenberg's observation that overactivity is as much a pathologic sign as underactivity and is probably more frequent.

Further inspection of line C, columns 2, 3, 4 and 5, reveals that there is no difference in average activity of the Mayer response between groups of patients with an active corneal reflex and patients with an inactive corneal reflex. However, the index of the activity of the Mayer reflex is much higher for patients with an active pharyngeal reflex than for patients with an inactive pharyngeal reflex, and the difference is significant to the 1.2 per cent level (C. R. = 2.5). In other words, among patients without organic disease of the brain, on the average, an active pharyngeal reflex implies an active Mayer reflex, and an inactive pharyngeal reflex implies an inactive Mayer reflex. To this point, the values with respect to the Mayer reflex closely parallel those with respect to the abdominal reflex. Among patients with organic disease of the brain (line E) there is no difference in average activity of the Mayer reflex between patients with an active pharyngeal reflex and patients with an inactive pharyngeal reflex. However, there is a considerable difference in the average activity of the Mayer reflex between patients with an active corneal reflex and patients with an inactive corneal reflex, respectively, and this difference is significant to the 0.5 per cent level (C. R. = 2.8). Thus, among patients with organic disease of the brain, patients with an inactive

corneal reflex, on the average, exhibit an active Mayer response more frequently than those with an active corneal reflex.

We are now in a position to formulate and test criteria for the interpretation of the Mayer reflex. If among organically normal patients the activity of the Mayer reflex may be expected to vary with the activity of the pharyngeal reflex, then it is justifiable to infer that an inactive Mayer response in the presence of an active pharyngeal response is highly significant of disease of the brain. On line F, columns 4 and 5, it is seen that 86 per cent of the patients in this series with an inactive Mayer reflex but with an active pharyngeal reflex have organic disease of the brain (6 of 7), as against 15 per cent of those with an inactive Mayer reflex and an inactive pharyngeal reflex (5 of 34); an inactive Mayer reflex is almost six times as significant for organic disease of the brain in the presence of an active pharyngeal response as in the presence of an inactive response (C. R. = 4.6). Line G reveals that an overactive Mayer response cannot be evaluated in terms of the pharyngeal response, since the incidence of organic cerebral disease is almost the same whether the pharyngeal reflex is active or inactive. However, in this case, the corneal reflex becomes a useful criterion. Among patients with an overactive Mayer response, organic disease of the brain is two and one-half times as frequent in the presence of an inactive corneal reflex as in the presence of an active corneal reflex, and this difference is highly significant (C. R. = 3).

The suggested criteria for interpreting the Mayer reflex may be stated as follows: When the Mayer reflex is absent or is only slightly active, organic disease of the brain is highly probable if the pharyngeal reflex is active; when the Mayer reflex is extremely (or perhaps moderately) active, organic disease is highly probable if the corneal reflex is inactive.

It will be recalled that in the preceding section a distinction was made between the combination of an inactive corneal and an active pharyngeal reflex, on the one hand, and an underactive abdominal and an active pharyngeal reflex, on the other. The first pair suggests organic disease of the brain only because, on the basis of the incidence of the two signs taken individually, the combination is to be expected relatively infrequently in the absence of organic disease of the brain. The second pair suggests organic disease of the brain, because in the presence of a normal brain there is the physiologic basis for a direct relation between activity of the abdominal and of the pharyngeal reflex; therefore any deviation from this relationship in the indicated direction suggests disease. The data may now be examined to discover which type of relationship is the basis for the criteria we have just ascertained for interpretation of the Mayer reflex. From line H, organic disease

appears to be 54/38 times as frequent in the presence of an inactive corneal reflex as in the total population. From column 1, organic disease appears to be 52/38 times as frequent in the presence of an active Mayer reflex as in the total series. One has a right, then, to expect, on the basis of probability alone, without necessarily inferring a physiologic relationship, that the combination of an inactive corneal and an active Mayer reflex will provide an incidence of organic disease equal to 54/38 by 52/38, multiplied by the incidence of organic disease in the general population (38 per cent). This product is 74 per cent, which agrees closely with the observed incidence of 79 per cent. We must conclude that the inverse relationship between activity of the corneal reflex and activity of the Mayer reflex among patients with organic disease of the brain is a statistical one only. Again, from line H, organic disease is 65/38 times as frequent in the presence of an active pharyngeal reflex as in the total population. From column 1, organic disease is 27/38 times as frequent in the presence of an inactive Mayer reflex as in the total population. Again, on the basis of probability alone, the incidence of organic disease of the brain in cases in which the Mayer reflex is inactive and the pharyngeal reflex active is expected to be 65/38 times 27/38, multiplied by the incidence of organic disease in the total population (38 per cent). This product is only 46 per cent, in contrast to the observed incidence of 86 per cent, a difference which is significant to the 0.9 per cent level (C. R. = 2.6). We must infer, therefore, that the pathologic significance of the inactive Mayer reflex in the presence of the active pharyngeal reflex depends not on statistical incidence but on a physiologic antagonism between these two values in the absence of organic disease of the brain.

5. *Relation of the Corneal and Pharyngeal Reflexes to the Babinski Reflex.*—Positive Babinski responses (extension of the large toe) were, of course, more frequent among our patients with organic disease of the brain than among the patients without organic disease of the brain. There is not a sufficient number of frank positive responses in the series, however, to permit the type of analysis made in the case of abdominal and Mayer reflexes. Nevertheless, the records include 42 patients with no response to plantar stimulation and 81 patients with the plantar flexor response. Although it might have been expected, on the basis of analogy with the previously discussed phenomena, that similar relations with corneal and pharyngeal reflexes would appear, actually no correlations were even vaguely apparent. The only possible exception to this is a somewhat suggestive association between absence of the plantar response and absence of the corneal reflex among patients with organic disease of the brain—an entirely statistical phe-

nomenon and one whose absence would be more surprising than its presence.

6. *Relation of Corneal and Pharyngeal Reflexes to Deep Reflexes and the Hoffmann Reflex.*—It is fairly well established that a positive Hoffmann reflex is merely an exaggerated tendon reflex (Wartenberg [5]); our results are consistent with this thesis in that neither the deep reflexes nor the Hoffmann reflex showed any relation to either the corneal or the pharyngeal reflex. A population of 141 patients, of whom 21 per cent had organic disease of the brain, was available for study of deep, or tendon, reflexes. Of patients whose tendon reflexes seemed of about average activity, 6 per cent had organic disease of the brain; of patients with underactive reflexes, 14 per cent had such disease; of patients with diffusely overactive reflexes, 22 per cent exhibited signs of organic cerebral disease, and of patients with irregular distribution of tendon reflex activity, 33 per cent had organic disease of the brain. These ratios were not significantly different when patients were grouped according to the activity of their corneal and pharyngeal reflexes.

Of even greater interest is the fact that in the population here studied the Hoffmann response proved of no assistance in distinguishing cases of organic disease of the brain, since there was an equal proportion of patients with organic disease who exhibited positive and negative Hoffmann responses. No matter what type of analysis is employed, the data show nothing but a random distribution when the cross classification is made on the basis of Hoffmann response and the corneal or the pharyngeal responses. We agree categorically with Wartenberg's recent statement:

> It is essential to stress that however valuable a pyramidal sign the Hoffmann reflex may be, it is not itself pathologic; it indicates, if outspoken, only a state of increased muscular tonus, which may be pyramidal, but may also be purely functional, and therefore is diagnostically insignificant.[5]

On the basis of these results, it may be inferred that exaggeration of the deep reflexes and a positive Hoffmann response, on the one hand, and absence of the abdominal reflex and the Mayer reflex, on the other, achieve their clinical significance by different mechanisms, although both groups of signs are considered indicative of damage to the pyramidal tract. This inference is consistent with recent experimental work.[7]

7. *Relation of the Pharyngeal Reflex to Muscular Tonus.*—Muscular tonus was tested by estimating roughly the resistance offered to passive manipulation of the upper extremities and was recorded as normal (or,

7. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

better still, average) and slightly, moderately or greatly increased or decreased. Index numbers were constructed by averaging assigned values: 0 for average tonus; 100, 200 and 300 for slightly, moderately and greatly increased tonus, respectively, and — 100, — 200 and — 300 for the three grades of diminished tonus. Among the patients without organic disease of the brain, those with an active pharyngeal reflex averaged — 10 for tonus, and the group with an inactive pharyngeal reflex averaged + 44. This difference, while not sufficiently clearcut to be of clinical usefulness, is nevertheless significant to the 1.6 per cent level (C. R. = 2.4). No association with the corneal reflex was discernible.

8. *Relation of the Corneal Reflex to Tremor.*—The presence of tremor was tested for by inspection of the outstretched upper extremities and was recorded as absent, slight, moderate, marked. Index numbers were constructed in the usual manner by assigning respective values of 0, 100, 200 and 300 to the four groups and averaging. Among the patients without a diagnosis of organic disease of the brain, those with an active corneal reflex averaged 53, and those with an inactive corneal reflex averaged 91. As in the preceding paragraph, this difference is not sufficiently conspicuous to be of clinical value, but it does reach the level of significance of 1.6 per cent (C. R. = 2.4). No association with the pharyngeal reflex was evident.

9. *Relation of Corneal Reflex to Spontaneous Motility.*—Proceeding from the elementary and automatic fragments of behavior to its more complicated and derived aspects, estimations become less precise and correlations more equivocal. The patient's spontaneous motility was rated on the basis of restlessness and frequency of random and purposive movements and was graded as normal or slightly, moderately or greatly increased or decreased. Indexes were computed by the method described in section 7. Of 110 patients without organic disease of the brain, the average motility index for the group with active corneal reflexes is 69 and for the group with inactive corneal reflexes 29. Since this type of estimation is less precise than the grading of reflex responses, standard deviations are higher and the critical ratio in this instance is only 1.74; i. e., the relationship is significant only to the 9 per cent level (odds for significance, 10:1). No definite conclusion can be drawn.

10. *Relation of Corneal and Pharyngeal Reflexes to Clinically Estimated Aggressiveness.*—After the psychiatric interview, each patient was recorded as aggressive, resistive or submissive in attitude toward the examiner. This was done in the sanguine hope that an elementary fraction of behavior might thus be recorded. Values of — 100, 0 and 100 were assigned to the three groups, respectively, and

indexes constructed as previously. The index numbers for the four CP groups of patients without organic disease of the brain were 37, 62, 100 and 63, respectively. The only difference apparent was that between the C + P + group and the other three groups taken together (average 65). However, computation revealed that the critical ratio for this difference is only 1.4, a value insufficient for the establishment of correlation.

11. *Relation of the Pharyngeal Reflex to Autism.*—Autistic phenomena, either hallucinatory or delusional, were recorded as none, slight, moderate or marked, and indexes were computed on this basis. Of the patients without organic disease, those with an inactive pharyngeal reflex seemed to show, on the average, more autism than those with an active pharyngeal reflex, and computation here elicited a critical ratio of 2.1, i. e., a level of significance of 3 per cent. It is likely that this is the same correlation as was found between schizophrenic activity and obtundation of the pharyngeal reflex (section 2).

12. *Relation of Corneal and Pharyngeal Reflexes to Conversion Symptoms.*—The problem of absence of the corneal and pharyngeal reflexes with conversion hysteria was one of the motivating factors in the organization of this study. Since no patient was included for whom the sole diagnosis was conversion hysteria, the question could not be answered directly. However, 21 patients out of 100 who were free from organic disease of the brain exhibited conversion phenomena as part of their symptoms. The percentage incidence of these patients in the four CP groups is 30, 18, 0 and 24; no relationship between either the corneal or the pharyngeal reflex and conversion symptoms appears in this series.

13. *Relation of Corneal and Pharyngeal Reflexes to Anxiety.*—Anxiety, too, was regarded as a more or less elementary aspect of behavior, and it was estimated for each patient after psychiatric interview, on the basis merely of general impression. The usual gradations and index numbers were assigned. In addition, several of the somatic concomitants of anxiety, such as pulse rate, systolic, diastolic and pulse pressure, palmar sweating and hand temperature, were evaluated on a more exact basis. The activity of the corneal and pharyngeal reflexes bore no relation either to anxiety or to any of these somatic factors.

14. *Relation of Corneal and Pharyngeal Reflexes to Affect.*—Affect was tentatively assumed to be a unitary aspect of behavior, and its quantitative variations were recorded and graded in the usual fashion. The criteria employed in estimating variations were not definite but included the usual clinically evident data, such as the interest of the patient in his present situation, his enthusiasm with respect to plans for the future, facial mobility and vivacity of vocal expression. Depres-

sive syndromes were classified with manic ones as forms of affective exaggeration. An attempt was made to distinguish apprehensiveness and anxiety, such as appear frequently in catatonic patients, from true affective exacerbation or obtundation. Obviously, the precision of these estimates could not be very high, and resultant coefficients of variation are considerable. Nevertheless, among patients without organic disease of the brain the average rating of affect for the group with active pharyngeal reflex is —31, while for patients with inactive pharyngeal reflex the average rating of affect is — 123. This difference is significant to the 0.9 per cent level (C. R. = 2.6). It would seem, therefore, that there is an association between inactivity of the pharyngeal reflex and affective impairment, at least among the patients in this series.

SUMMARY AND CONCLUSIONS

The pharyngeal reflex has been found to indicate the lower limit of normal activity for abdominal and Mayer reflexes. Thus, in the absence of organic disease of the brain, an active pharyngeal reflex implies an active abdominal and an active Mayer reflex. Similarly, in the presence of an inactive pharyngeal reflex, underactivity of the abdominal and Mayer reflexes is not necessarily indicative of disease.

The concurrence of an active pharyngeal and an inactive corneal reflex and the concurrence of an overactive Mayer and an inactive corneal reflex have been found to be much less frequent among patients with organically sound brains than among patients with organic disease of the brain. Thus, although these two combinations are not positive signs of abnormality, they are highly suggestive.

Obtundation of the pharyngeal reflex is found to be statistically associated with an attitude some of the manifestations of which include affective blunting, autistic thinking and schizophrenic activity.

Criteria for the interpretation of the Mayer reflex have been suggested: Absence of or a weakly active Mayer response is indicative of a pathologic process if the pharyngeal reflex is active; a brisk Mayer response is usually indicative of a pathologic process if the corneal reflex is inactive.

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HEREDITARY SCLEROSES

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THE term "heredofamilial" should be applied only to those diseases which are due to a change in the chromosomes which persists for several generations. They may also be called heredodegenerative (Jendrassik [1]), since they all represent a minus variant. Unlike these persisting changes of the chromosomes, the mutations, which cause heredofamilial diseases, the paravariations, originating under the influence of the surroundings, and the mixovariations, changes due to the union of two genes of different character, are not hereditary.

The properties of a man that are due to the structure of the idioplasm are called constitutional (genotypical, idiotypical). In addition to these inherited properties, there are others acquired in fetal life or after the birth; they were termed "conditional" by Tandler.[2] The phenotypical man thus represents a combination of constitutional and conditional factors. A factor of either type may lead to disease when it deviates from the norm. When the constitutional factor prevails, amounting to 50 per cent or more, one speaks of a constitutional disease; to this type belong the heredodegenerative diseases. The conditional diseases include, among others, various fetal diseases that lead to congenital, and even familial, disorders. It should be emphasized that the terms "congenital" and "familial" do not mean heredofamilial, since congenital or familial diseases may also be caused by external factors.

It is probable that mutations may occasionally be produced by chronic alcoholism or other poisoning and by physical forces (e. g., roentgen rays). Yet such instances are too rare to account for the mutations in man in general. In an attempt to find the cause of the mutations in amaurotic familial idiocy, I assumed, in view of the frequency of diabetes in the ancestry, that acidosis plays an important role. Katase,[3] by feeding saccharose to rabbits, obtained various monsters in

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1. Jendrassik: Die heredodegenerativen Nervenkrankheiten, in Lewandowsky, W.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 231.

2. Tandler, J.: Konstitution und Rassenhygiene, Ztschr. f. ang. Anat. **1**:11, 1913.

3. Katase: Experimentelle Studien über die Entstehung des Hydrocephalus und die Entwicklungsanomalien des Auges, Tr. Soc. path. japon. **25**:583, 1935.

the first, and even more in the second, filial generation and thus furnished evidence of a mutation due to acidosis.

It is unlikely that disease is transmitted as such directly. Rather, there is a change of the soma, with predisposition to a disease; but the various particular constitutions are not yet well understood. No doubt the individual constitution, largely determined by the endocrine glands, plays a major role, leading to various generalized, metabolic and vascular trophic changes. I [4] studied the endocrine constitution in cases of amaurotic familial idiocy and observed changes in the adrenal system and the thymus, resembling those described by other authors.

A great difficulty in applying to man the rules of heredity in plants, as established by Johann Gregor Mendel [5] is the comparatively small number of children per subject. Further, the inherited peculiarities are complicated in man, since they are due to changes in the chromosomes of many ancestors. Hence, a comparison with the simple color changes in plants is not possible. Finally, the diseased descendants may die in early childhood, without being able to produce a new generation.

The only conclusion possible may be expressed as follows: Different persons with similar constitutions under similar conditions may exhibit the same disease. It is, further, more likely that similar constitutions will appear in two or more descendants of a consanguineous marriage, in which the parents may possess homologous genes, homozygotes, than in descendants of a marriage between persons of different ancestry (heterozygotes). Certainly, there are heredodegenerative diseases of the nervous system. The factor of heredity may be dominant; that means the disease is the same in all affected generations; it may be recessive, i. e., transmitted by a healthy parent, or it may be mixed. Such diseases may, further, be sex bound; they may be of the same type (homotypic); they may occur at the same site (homotopic), and they may develop at the same time of life (homochronous). Particularly, the time-bound appearance of certain diseases is not easy to explain, since it does not always coincide with the various evolutional or involutional phases. Certainly, however, the time factor is important in the constitution.

Before applying the foregoing considerations to the heredofamilial scleroses, one has to establish the types of sclerosis that belong in this group. Since scleroses represent glial proliferations replacing destroyed parenchyma, one should include in this term neither the tumor-like proliferations of mature tissue nor those of blastomatous tissue. There-

4. Marburg, O.: The Endocrine Glands in Infantile Amaurotic Idiocy, J. Nerv. & Ment. Dis. **100**:450, 1944.

5. Mendel, G.: Versuche über Pflanzenhybriden, Verhandl. naturf. Ver., in Brünn, 1865.

fore Neubürger's [6] suggestion, accepted by other authors, that there are blastomatous, degenerative and inflammatory types of diffuse sclerosis, should be rejected, in agreement with Bielschowsky and Henneberg,[7] who assumed the existence of a degenerative and an inflammatory form only, the former being endogenous and the latter exogenous. The familial occurrence of diffuse sclerosis is by no means evidence of a heredofamilial degeneration, for the simultaneous involvement of two or more members of a family may be caused not only by a constitutional but by an exogenous factor. On the other hand, Guttmann [8] went too far in absolutely denying the existence of a degenerative form, which he assumed to be just a variant of the inflammatory type. Suffice it to mention the investigations of Marburg and Casamajor [9] demonstrating the relationship of diffuse sclerosis to phlebostasis and phlebothrombosis, whereby a serous profusion may be the cause of the parenchymal destruction, followed by a sclerotic process. Accordingly, scleroses are proliferations of glia which follow destruction of the myelin sheath, with comparatively well preserved axons.

There are various types of scleroses, according to the distribution and the character of the disease. In 1906 I [10] suggested calling acute sclerosis with demyelinating processes "encephalomyelitis periaxialis scleroticans." The principle of this terminology was accepted by Schilder [11] for diffuse sclerosis: encephalomyelitis periaxialis diffusa. Since there are degenerative and inflammatory forms, one should designate the degenerative forms as "encephalopathia periaxialis disseminata" and "encephalopathia periaxialis diffusa," respectively, and the inflammatory forms as "encephalomyelitis periaxialis disseminata" and "encephalomyelitis periaxialis diffusa," respectively. These terms have not been accepted generally. As for the inflammatory forms of acute multiple sclerosis, they are characterized by hyperemia, as well as by exudation from the blood vessels, associated with demyelination in the same region. These manifestations justify calling the process inflammatory, a term which

6. Neubürger, K.: Histologisches zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:336, 1921.

7. Bielschowsky, M., and Henneberg, R.: Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva), J. f. Psychol. u. Neurol. **36**:131, 1928.

8. Guttmann, E.: Die diffuse Sklerose, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:1, 1925.

9. Marburg, O., and Casamajor, L.: Phlebostasis and Phlebothrombosis of the Brain in Newborn and in Early Childhood, Arch. Neurol. & Psychiat. **52**:170 (Sept.) 1944.

10. Marburg, O.: Die sogenannte akute multiple Sklerose (Encephalomyelitis periaxialis scleroticans), Leipzig, F. Deuticke, 1906.

11. Schilder, P.: (*a*) Zur Kenntnis der sogenannten diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912; (*b*) Die Encephalitis periaxialis diffusa, Arch. f. Psychiat. **71**:327, 1924.

in this connection designates a histologic syndrome and does not indicate the etiologic factors (toxic, infectious or reactive). The same holds true for the acute form of diffuse sclerosis, as Schilder,[11] Bielschowsky and Henneberg[7] and others also stated. It is not easy to establish whether the inflammatory process is primary or secondary (symptomatic).

Thus, one must distinguish the following groups of heredofamilial sclerosis:

Multiple sclerosis { (*a*) Encephalopathia periaxialis disseminata; (*b*) Encephalomyelitis periaxialis disseminata

Diffuse sclerosis { (*a*) Encephalopathia periaxialis diffusa; (*b*) Encephalomyelitis periaxialis diffusa (Schilder's disease)

Combined sclerosis

Pelizaeus-Merzbacher disease (degenerative form only)

MULTIPLE SCLEROSIS

About 100 cases of the familial type have been observed, in most of which no pathologic examination was made. The majority of cases were instances of the familial type only, not the heredofamilial disease. Only 4 cases were instances of the heredofamilial type: 1 case reported by Eichhorst[12] (mother and son); later, another case from the same author,[13] in which the mother of the patient had spastic spinal paralysis; a case reported by Haber[14] (brother and sister, the parental grandmother of whom had a disease of the spinal cord), and a case reported by Thomas[15] (mother and daughter) studied pathologically by Gournand.[16] It is impossible to recognize a particular type of heredity in these cases. Unfortunately, these authors merely mentioned the anatomic picture of multiple sclerosis, without going into details. Gournand,[16] alone, clearly demonstrated acute multiple sclerosis in the case of Thomas.[15]

DIFFUSE SCLEROSIS

Einarson and Neel,[17] as well as Bielschowsky and Henneberg,[7] distinguished the following types of heredodegenerative (familial) diffuse sclerosis: (*a*) acute infantile (Krabbe[18]), (*b*) subacute juvenile (Scholz[19]), (*c*) adult (Ferraro[20]) and (*d*) chronic (Pelizaeus,[21] Merzbacher[22]).

12. Eichhorst, H.: Ueber infantile und heriditäre multiple Sklerose, Virchows Arch. f. path. Anat. **146**:173, 1896.

13. Eichhorst, H.: Multiple Sklerose und spastische Spinalparalyse, Med. Klin. **40**:1617, 1913.

14. Haber, T.: Kasuistische Mitteilung zur Frage des hereditären Auftretens der multiplen Sklerose, Monatschr. f. Psychiat. **51**:226, 1922.

15. Thomas, A.: Sclérose en plaques chez mère et la fille, Rev. neurol. **2**:714, 1929.

16. Gournand, A.: La sclérose en plaques aiguë, Paris, A. LéGrand, 1930.

17. Einarson, L., and Neel, A. V.: Notes on Diffuse Sclerosis, Diffuse Gliomatosis and Diffuse Glioblastomatosis of the Brain, with a Report of two Cases, Copenhagen, Ejnar Munksgaard, 1940.

(Footnotes continued on next page)

The number of cases of heredofamilial and familial diffuse sclerosis is comparatively small. Van Bogaert and Scholz [23] found only 15 cases of the familial type, involving 5 families, among 70 cases of diffuse sclerosis. In reviewing the literature, I found the acute infantile type in 7 families: 2 cases of Krabbe,[18] 1 case of Van Bogaert and Scholz,[23] 1 case of von Eiselsberg,[24] 1 case of Russel and Tallermann,[25] 1 case of de Lange [26] and 1 case of Josephy and Lichtenstein [27] (though in the last case the disease was not acute). The subacute juvenile type was present in 9 families: the cases of Haberfeld and Spieler,[28] Schilder,[11b] Scholz,[19] Bielschowsky and Henneberg,[7] Symonds [29] (2 families), Curtius,[30] Walthard [31] (case in the same family as that of Scholz) and Meyer and Tennent [32] (2 families). Of the adult type only Ferraro's [20] cases are

18. Krabbe, K.: A New Familial, Infantile Form of Diffuse Brain Sclerosis, Brain **39**:74, 1916.

19. Scholz, W.: Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer diffuser Hirnsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:651, 1925.

20. Ferraro, A.: Familial Form of Encephalitis Periaxialis Diffusa, J. Nerv. & Ment. Dis. **66**:329, 479 and 616, 1927.

21. Pelizaeus, E.: Ueber eine eigentümliche Form spastischer Lähmung mit Cerebralerscheinungen auf hereditärer Grundlage (multiple Sklerose), Arch. f. Psychiat. **16**:201, 1885; **31**:100, 1899.

22. Merzbacher, L.: Eine eigenartige familiär-herditäre Erkrankungsform (Aplasia axialis extracorticalis congenita), Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

23. van Bogaert, L., and Scholz, W.: Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiären diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:510, 1932.

24. von Eiselsberg, F.: Ueber frühkindliche familiäre diffuse Hirnsklerose, Ztschr. f. Kinderh. **58**:702, 1937.

25. Russel, D., and Tallermann, K.: Familial Progressive Diffuse Cerebral Sclerosis of Infants, Arch. Dis. Childhood **12**:71, 1937.

26. de Lange, C.: Ueber die familiäre infantile Form der diffusen Hirnsklerose, Ann. pædiat. **154**:140, 1939-1940.

27. Josephy, H., and Lichtenstein, B. W.: Diffuse Leukoencephalopathy Without Sclerosis, Arch. Neurol. & Psychiat. **50**:575 (Nov.) 1943.

28. Haberfeld, W., and Spieler, F.: Zur diffusen Hirn- und Rückenmarksklerose im Kindesalter, Deutsche Ztschr. f. Nervenh. **40**:436, 1910.

29. Symonds, O. P.: A Contribution to the Clinical Study of Schilder's Encephalitis, Brain **51**:24, 1928.

30. Curtius, F.: Familiäre diffuse Sklerose und familiäre spastische Spinalparalyse in einer Sippe, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:209, 1930.

31. Walthard, K. M.: Familiäre diffuse Hirnsklerose, Schweiz. Arch. f. Neurol. u. Psychiat. **32**:251, 1933.

32. Meyer, A., and Tennent, T.: Familial Schilder's Disease, Brain **59**:100, 1936.

known, and, in addition, the case of a family reported by van Bogaert and Nyssen.[33] Finally to the chronic type belong the cases of Pelizaeus [21] and Merzbacher [22]; in the same family, the cases of Spielmeyer [34] and of Liebers,[35] and a case of Bodechtel.[36] In the cases enumerated, autopsy was performed on at least 1 member of the family. On the whole, this is a relatively small figure as compared with the number of cases of the nonfamilial disease.

Heredity.—In cases of the disease in early childhood, though occurring in a familial manner, no specific heredity is exhibited. There are no nervous diseases among the ascendants. The same holds true for the adult type. In cases of the juvenile type a nervous disease may be present in one of the parental generations; in addition, there may be a history of alcoholism or tuberculosis. The latter conditions are occasionally also observed in the ascendants in cases of the infantile type. Scholz [19] first reported the occurrence of spastic spinal paralysis in a parental generation; the first filial generation was free of nervous diseases; in the second filial generation diffuse sclerosis appeared. However, Scholz [19] was not absolutely sure about the diagnosis of spastic spinal paralysis. This same disease was described among the ascendants by Curtius.[30] Whereas Scholz [19] did not exclude the possible diagnosis of multiple sclerosis, Meyer and Tennent [32] described with certainty the occurrence of multiple sclerosis among the ascendants. In any case, diffuse sclerosis exhibits recessive heredity, so that the disease causing the heredofamilial degeneration has not yet been revealed. It probably belongs to the sclerosis group. The only type of diffuse sclerosis with definite heredity is Pelizaeus-Merzbacher disease. The heredity resembles that of hemophilia; the disease is transmitted from a healthy female with a diseased brother to males in the filial generation. Since not all familial disorders are heredodegenerative, the number of cases of true heredodegenerative diffuse sclerosis is even smaller than the number of the familial type.

Structure.—Schaffer [37] stressed that structure analysis is necessary to classify a case of sclerosis as of the heredofamilial type. Thus, I

33. van Bogaert, L., and Nyssen, R.: Le type tardif de leukodystrophie familiale, Rev. neurol. **65**:21, 1936.

34. Spielmeyer, W.: Der anatomische Befund in einem zweiten Fall von Pelizaeus-Merzbacherscher Krankheit, Zentralbl. f. d. ges. Neurol. u. Psychiat. **32**:203, 1923.

35. Liebers, M.: Zur Histopathologie des zweiten Falles von Pelizaeus-Merzbacherscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:487, 1928.

36. Bodechtel, G.: Zur Frage der Pelizaeus-Merzbacherschen Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:487, 1939.

37. Schaffer, K.: Ueber das morphologische Wesen und die Histopathologie der herditär-systematischen Nervenkrankheiten, Berlin, Julius Springer, 1926.

studied 2 cases,[38] 1 of type *a* and another of type *b*, and found the most striking feature to be the extension of the process, the diffuse demyelination of the centrum ovale. There is, however, a wide range of variations. Occasionally almost the entire white matter is affected (fig. 1 *A*), from the frontal to the occipital lobe, as in the case of Meyer and Tennent [32]; in other cases some lobes are spared. One must agree with Bouman [39] that the occipital, parietal and temporal regions are more frequently affected than is the frontal region. There may be patches of complete demyelination (fig. 1 *B*); in other cases there is the picture of foci of myelin shadows, and concentric demyelination has been reported. On

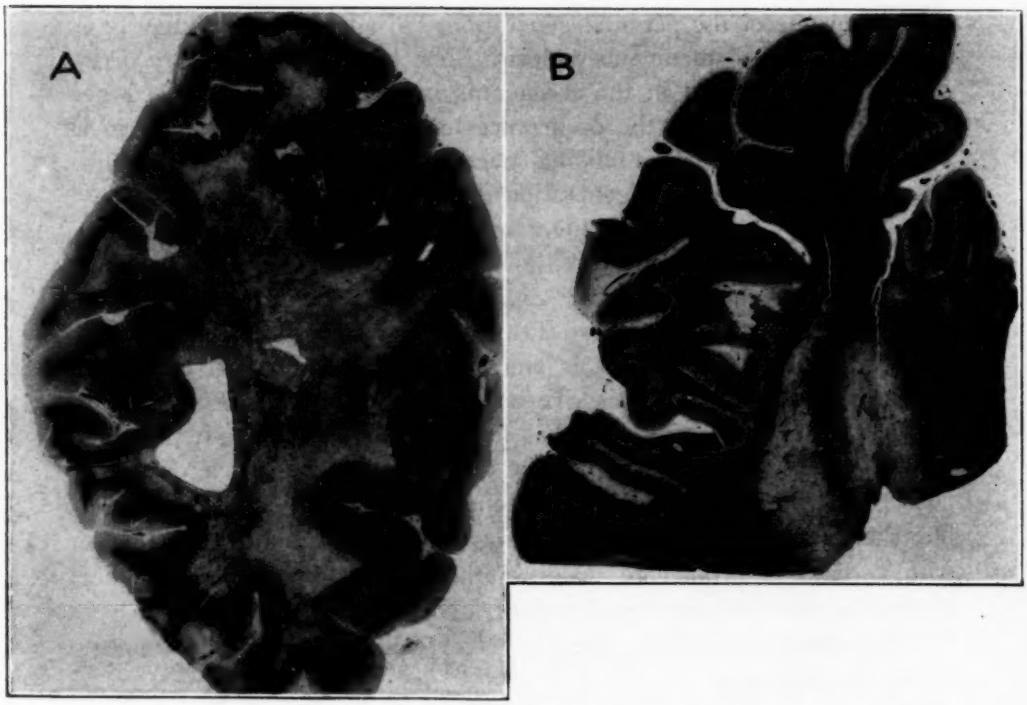

Fig. 1.—*A* (case 2), diffuse sclerosis, with U fibers intact. *B* (case 1), diffuse sclerosis (type of Krabbe), with two large foci.

accurate examination one will find, in addition to large areas of demyelination, small ones at the periphery, resulting in a pathologic picture resembling that of multiple sclerosis, in spite of the presence of large areas of destruction. The resemblance to multiple sclerosis is also indicated by the persistence of single myelin fibers or of groups of such fibers within the large foci. In some cases the demyelination presents

38. The cases referred to which I reinvestigated were those of von Eiselsberg (case 1) and Pfleger (case 2) (Jahrb. f. Psychiat. u. Neurol. **50**:142, 1933).

39. Bouman, L.: Diffuse Sclerosis, Bristol, John Wright & Sons, Ltd., 1934.

sharp borderlines; in others there is a gradual transition into normal tissue, in which the border fibers may be swollen or present a rosary-like appearance, or they may be partly degenerated.

Most authors have stressed the intactness of the U fibers (fig. 1 *A*), which is observed in many cases. Occasionally, however, the ring of the U fibers is perforated at one point or another. Nevertheless, the picture of intact U fibers, with a normal overlying cortex, is characteristic.

It is not only the centrum ovale which is affected. In many cases the striopallidum (von Eiselsberg,[24] Russel and Tallermann [25]) and the optic thalamus (Liebers [35]) show similar lesions, and frequently the optic nerve is also involved (Krabbe,[18] Scholz,[19] Bielschowsky and Henneberg,[7] Russel and Tallermann,[25] Ferraro [20] and others). The cerebellum frequently is the site of a focus (Russel and Tallermann,[25] Ferraro [20]); and the brain stem, as well as the spinal cord, may be affected (von Eiselsberg,[24] Russel and Tallermann,[25] de Lange [26]). Thus, in most cases the disease approaches multiple sclerosis as far as the distribution of lesions is concerned. In the cases with localization in the brain stem, as well as in cases with foci in the centrum ovale, sometimes sharp, sometimes hazy, borderlines are observed.

In spite of the total demyelination, a number of axons, though usually few, may be relatively well preserved. Their number depends on the character of the focus. In an acute process, indicated by the presence of many compound granular cells, one finds comparatively many intact axons; in foci with far advanced sclerosis or with regressive changes no axons are encountered. In many cases, however, the destruction of the myelin sheaths is not commensurate with that of the axons, which may disappear even in cases of the chronic (Pelizaeus-Merzbacher) type. Some foci, particularly those in the optic chiasm, closely resemble the foci of multiple sclerosis (Liebers [35]).

There are areas deprived almost completely of oligodendrocytes; the few present are degenerated (fig. 2). The ground substance is represented by a fine network of glial fibrils. In other areas there are giant astrocytes around a blood vessel; these cells are occasionally deprived of their processes. In general, the number of these giant cells is smaller than normal (fig. 3). At the border zones of the areas of sclerosis there is an increase in the number of the glia cells, some of which resemble the fetal cells of the sixth month, as depicted in Roback and Scherer's [40] paper on glial development (fig. 4). In this peripheral region one also encounters multinuclear cells (fig. 5), fibril-

40. Roback, H. N., and Scherer, H. J.: Ueber die feinere Morphologie des frühkindlichen Gehirns mit besonderer Berücksichtigung der Gliaentwicklung, Virchows Arch. f. path. Anat. **294**:365, 1935.

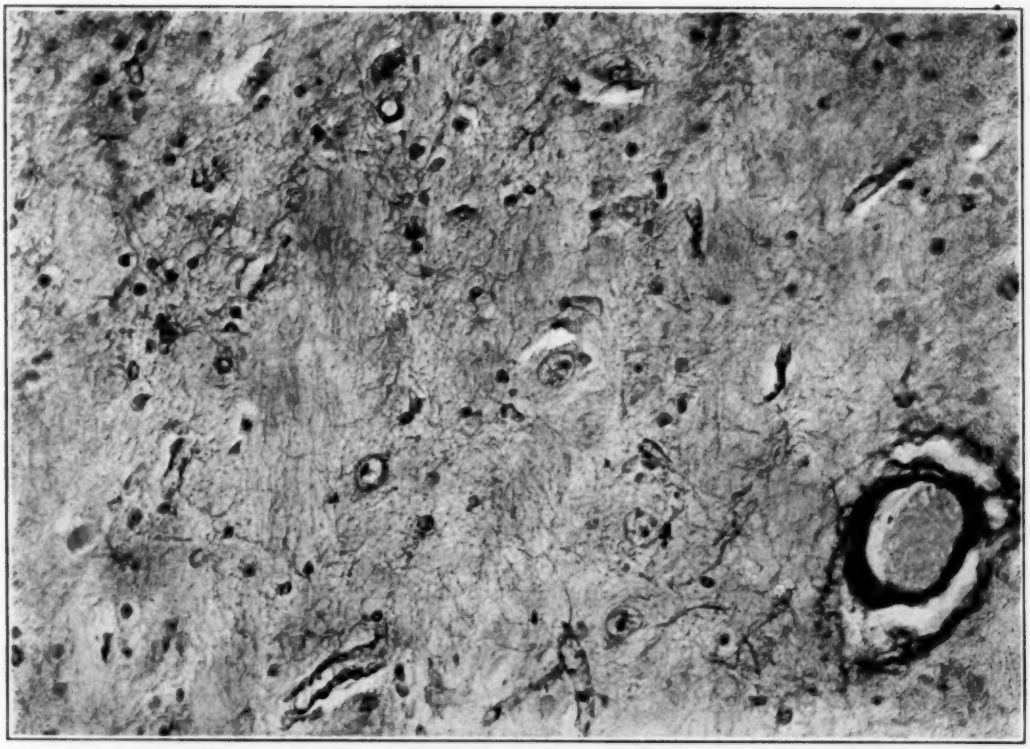

Fig. 2 (case 2).—Disappearance of oligodendroglia cells, vascular sclerosis.

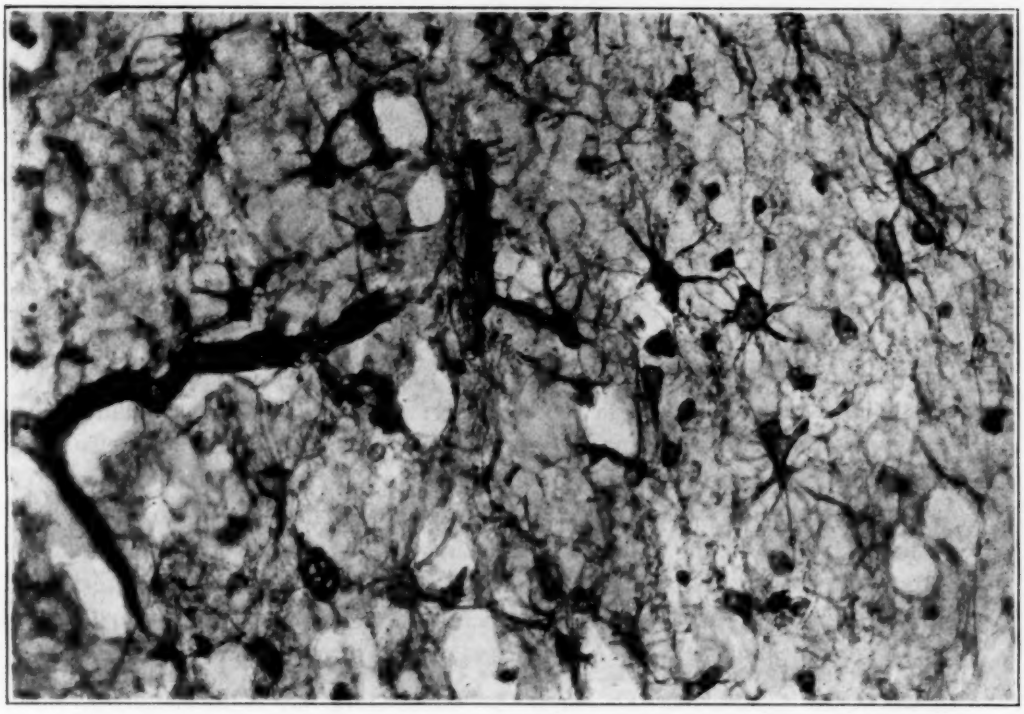

Fig. 3 (case 1).—Giant astrocytes in the center of a focus.

lary astrocytes and numerous compound granular cells. Cells of the last type are also seen in any fresh focus. Some of the large glia cells are transformed into *gemästete* cells (globoid cells), with small vacuoles in the cell body.

Though there are many signs of destruction of the glia, there is not an insufficiency of the glia as a whole, nor is there a clear manifestation of the existence of an endogenous process, as was assumed by Bielschowsky and Henneberg [7] and de Lange,[26] since exogenous causes may furnish a satisfactory explanation of the pathologic changes. In par-

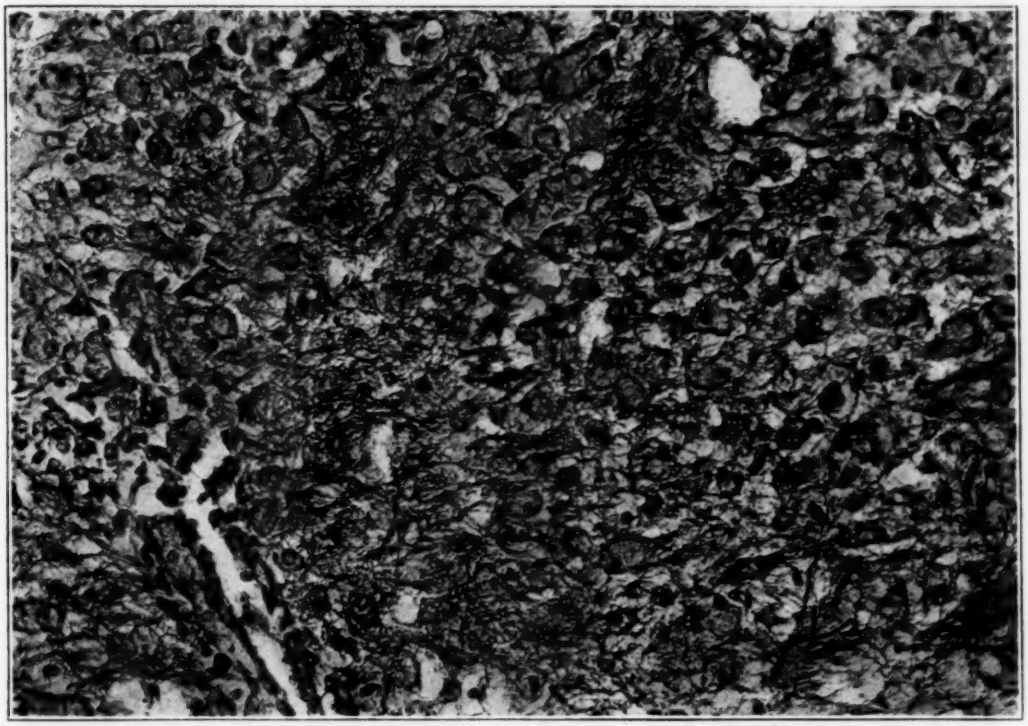

Fig. 4 (case 2).—Accumulation of different types of glia cells (fetal, globoid and compound granular).

ticular, there is no complete lack of the oligodendroglia, which was assumed by Collier and Greenfield.[41] This tissue is absent only in areas of complete disintegration. Further, contrary to the suggestion of Bielschowsky and Henneberg,[7] there is no insufficiency of the constructive apparatus, since there is intense fibrillogenesis, leading to anisomorphous sclerosis. Multinuclear glia cells, which, in the opinion of many authors, are evidence that these scleroses approach tuberous

41. Collier, G., and Greenfield, I. G.: The Encephalitis Periaxialis of Schilder, Brain **47**:489, 1924.

sclerosis, may be encountered also in cases of acute multiple sclerosis, together with globoid cells (*gemästete* cells).

The reaction of the mesoderm varies with the type of sclerosis. In the juvenile type there are perivascular infiltrations of lymphocytes, and occasionally of plasma cells. This exudate is the same as that described by me [10] in association with acute multiple sclerosis, and by Schilder [11a] with diffuse sclerosis. It depends on the point of view whether one

Fig. 5 (case 2).—Multinuclear glia cells.

calls the process symptomatic inflammation (Scholz [19]) or true inflammation (Meyer and Tennent,[32] in agreement with Haberfeld and Spieler [28] and Schilder [11a]). The changes in the vessel walls have scarcely been described. In regions close to the scleroses one encounters empty veins, the lumens of which are narrow in some places, as though contracted. In other areas the lumens are wide but empty (fig. 6). In necrotic areas some vessel walls are degenerated (fig. 2).

obviously a secondary feature. The pictures resemble those in cases of birth injury with phlebastosis and phlebothrombosis, as described by Casamajor and me.[9] Putnam and Alexander [42] also saw phlebothrombosis in cases of diffuse sclerosis.

Comment: In summary, one may state: There is usually a bilaterally symmetric, demyelinating process in the centrum semiovale, followed by sclerosis, with participation of glia cells, which show different stages of progressive and regressive changes, depending on the state of the vascularization. The process is not always restricted to the

Fig. 6 (case 2).—Veins close to a focus, empty and contracted at one spot, enlarged nearby.

centrum semiovale but occasionally affects also the striopallidum, the optic nerve and even the brain stem and the spinal cord. The character of the process is degenerative and occasionally inflammatory. Thus, use of the terms encephalomyelopathia periaxialis diffusa and encephalomyelitis periaxialis diffusa is justifiable, whereas the designation "scleroticans" describes the pathologic process.

42. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch. Neurol. & Psychiat. **41**:1087 (June) 1939.

Pathogenesis.—It is difficult to assume with Schilder [11a] an inflammatory process in the genesis of hereditary diffuse sclerosis, since the possibility of the transmission of such a process through generations is doubtful. Another view assumes an insufficiency of the oligodendroglia in the production of myelin. However, aside from the fact that usually the axons also are destroyed, it is known from the investigations of Roback and Scherer [40] that the immature glia aids in the process of myelination. Whereas Scholz [19] asserted that there was an insufficiency of all glia cells, Bielschowsky and Henneberg [7] upheld the theory of an insufficiency of the entire vascular, as well as the glial, constructive apparatus. This theory leaves unexplained why such a disturbance of the entire constructive apparatus becomes effective only in certain circumscribed areas and not throughout the neuraxis. None of the authors mentioned noted that the peculiar distribution of the foci is associated with the area of drainage of the great vein of Galen (Schwartz,[43] Schlesinger [44]). My investigations in collaboration with Casamajor [9] have demonstrated that phlebostasis and phlebothrombosis in the great vein of Galen lead to destruction of these areas, with subsequent sclerotic processes and with intactness of the U fibers. This theory receives support also from case 3 of Globus and Strauss [45]: The sister of the patient (in the same disease) showed (venous) thrombosis of the sinuses throughout the brain.

Not a single case of diffuse sclerosis is known in which the disease occurred in the ascendants, so that in this disease it is particularly true that "familial" does not mean "heredodegenerative." Type *a* (Krabbe) may be explained by conditional rather than by constitutional factors, while the constitutional factor cannot be excluded in type *b*. Guttmann and Bodechtel [46] and Guttmann [8] did not differentiate these two types.

Wohlwill [47] (1921) first showed that a process in the veins may cause areas of destruction and demyelination resembling those in diffuse sclerosis. In 1928 he [48] suggested that some dissolved, harmful sub-

43. Schwartz, P.: Die traumatischen Schädigungen des Zentralnervensystems durch die Geburt: Anatomische Untersuchungen, Ergebn. d. inn. Med. u. Kinderh. **31**:165, 1927.

44. Schlesinger, B.: The Venous Drainage of the Brain, with Special Reference to the Galenic System, Brain **62**:274, 1939.

45. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathia, Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

46. Guttmann, E., and Bodechtel, G.: Diffuse Encephalitis mit sklerosierender Entzündung des Hemisphärenmarkes, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**:601, 1931.

47. Wohlwill, F.: Zur Frage der Encephalitis congenita (Virchow), Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:360, 1921.

48. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

stances may diffuse into the nerve tissue, thus causing demyelination. In 1931 Putnam [49] and his co-workers stressed the importance of phlebothrombosis in demyelinating processes. Finally, Casamajor and I [9] demonstrated that phlebospasm may have the same effect. It may be that the process of diffusion is caused by the same change as is the venous spasm, viz., by the previous enlargement of the vessels, according to Ricker's [50] *Phasengesetz.* Thus, three different circulatory changes in the venous system may lead to a similar effect: phlebodilatation (prestasis) with diffusion, phlebothrombosis and phlebospasm. These circulatory changes are sufficient to account for the process as a whole, so that it is not necessary to assume a heredodegenerative factor. One should, however, attempt to determine the constitutional factors in this disease, which probably will disclose the cause of the venous changes. As for the endocrine constitution, there are some cases of amaurotic familial idiocy (Bielschowsky,[51] Globus,[52] Flatau,[53] Ostertag [54]) with demyelinations resembling those in diffuse sclerosis. One would, however, be mistaken in assuming an essential relationship between these two diseases. On the other hand, amaurotic familial idiocy may be complicated by involvement of the centrum ovale. Since the endocrine constitution in patients with amaurotic familial idiocy is complicated (one encounters destruction of the adrenal medulla, changes in the thymus and involvement of the intermediate cells of the gonads), and since nothing is known about these glands in cases of diffuse sclerosis, it is difficult to draw definite conclusions. Hampel [55] was the only one to observe a case of Addison's disease associated with a demyelinating process in the hemispheres. There are some clinical fea-

49. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

50. Ricker, G., and Regendanz, P.: Beiträge zur Kenntnis der örtlichen Kreislaufstörung, Virchows Arch. f. path. Anat. **231**:1, 1921.

51. Bielschowsky, M.: Zur Histopathologie und Pathogenese der amaurotischen Idiotie, J. f. Psychol. u. Neurol. **26**:125, 1920-1921.

52. Globus, J. H.: Ein Beitrag zur Histologie der amaurotischen Idiotie, Ztschr. f. d. ges. Neurol. u. Psychiat. **85**:424, 1923.

53. Flatau, E.: Encephaloleucopathia scleroticans progressiva, Encéphale **20**: 475, 1925.

54. Ostertag, R.: Amaurotische Idiotie mit Entwicklungsstörungen des Gehirns und Kleinhirnatrophie, Centralbl. f. Neurol. **39**:190, 1925; Arch. f. Psychiat. **75**:355, 1925.

55. Hampel, E.: Morbus Addisonii und sklerosierende Erkrankung des Hemisphärenmarks: Beitrag zu den Hirnveränderungen beim Morbus Addisonii und zum Kapitel der diffusen Sklerosen, Deutsche Ztschr. f. Nervenh. **142**:186, 1937.

tures (e. g., hirsutism) that also point to involvement of the adrenal system. However, these changes are of too slight a degree to be used as a basis for discussion of the relationship between the adrenal system and the changes in the venous system.

Pelizaeus-Merzbacher disease is now assumed to be a combination of diffuse and multiple sclerosis; there are, however, no reports on changes in the vascular system.

SUMMARY

Familial diseases may, but need not, be heredofamilial. Heredofamilial diseases are caused by mutations alone.

As for the scleroses, multiple sclerosis usually is an exogenous disease, though there are certainly cases of the heredofamilial type.

The infantile form of diffuse sclerosis does not exhibit any evidence of being heredofamilial. The juvenile form may be heredofamilial, or it may be exogenous, whereas Pelizaeus-Merzbacher disease apparently always is heredofamilial.

In all the types under discussion, a change in the venous system (phlebostasis, phlebothrombosis, phlebospasm) may be the cause of demyelination. The cause of the venous change itself has not yet been revealed.

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NARCOLEPSY

II. Theory of Pathogenesis of the Narcolepsy-Cataplexy Syndrome

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IN a careful review of the literature on narcolepsy, Wilson [1] found that authors had classified narcolepsy according to the following etiologic factors: (1) trauma; (2) toxi-infectious states, such as encephalitis; (3) epilepsy; (4) endocrine disturbances, such as obesity; (5) psychopathologic disturbances; (6) local lesions (vascular lesions, tumor), and (7) cryptogenic conditions. He criticized these categories because they were not mutually exclusive, because presumably "predisposing" factors may be only accompaniments and because the influence of trauma can be overrated. He argued, further, that autopsy had not been performed in any case to ascertain the existence of such groups and that pathologic information at one's disposal was derived from cases of prolonged or continuous sleep and not from cases of the true narcolepsy-cataplexy syndrome. Therefore, although many researches tended to point to the floor, sides and posterior end of the third ventricle as a part of the neuraxis the mechanisms of which are engaged in the function of sleep,[2] he abandoned the search for the cause of narcolepsy in discrete lesions in this region. He pointed out that sleep is such a complex process that to imagine that motor, sensory, psychic, respiratory, circulatory and other activities are all controllable by one ganglionic center in the hypothalamus puts a strain on physiologic belief. He concluded that the hypothalamic center could best be regarded as serving to control viscerosympathetic activities which must diminish for sleep to set in, but that the cortex and thalamus had to cooperate to bring sleep about.

WILSON'S FORMULATION

Wilson abandoned all former speculations concerning the cause of narcolepsy because of their inherent deficiencies. In making his own formulation he began with the premise that any explanation of the pathogenesis of the disorder must bring the apparently diverse phenomena of narcolepsy, cataplexy, sleep paralysis and catalepsy (trance)

1. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, London, Edward Arnold & Co., 1940.

2. Wilson, S. A. K.: The Narcolepsies, Brain **51**:63-109, 1928; Modern Problems in Neurology, London, Edward Arnold & Co., 1928.

into line, since the clinical fact of the common existence of these various disorders in the patient dictated it. His concept of the cause of the syndrome, although it contains deficiencies, which he points out, strives toward that end.

He began with cataplexy and stated that it evidently is not pathologic but is akin to what can be found on occasion in normal persons or in animals. As a sequel to emotional stimuli, of which perhaps the commonest is laughter, one may be "convulsed" or made "weak" or "helpless." Animals, though they lack the gift of laughter for the most part, may become "rooted to the spot" or "frightened out of their lives" in sudden fear, or they may run away. Thus the affective stimulus either excites or inhibits, or inhibition succeeds excitation. Wilson went on to say that, for some ill understood reason, in the case of cataplexy such stimuli seemed invariably to inhibit.

He found the attack of sleep paralysis of the narcoleptic person similar to the cataplectic attack. The same kind of inhibition spreading to the motor area, but not radiating to the cortical fields involving consciousness, must be assumed to account for the fact that the patient is awake though powerless. He viewed the trancelike cataleptic state seen in the narcoleptic patient as a lesser degree of inhibition radiating over the cortex, in which movement was inhibited not to the point of atonia, as in patients with catalepsy or sleep paralysis, but to the point of modification of plastic tone, i. e., catatonia. As for the fits of deep sleep, the narcoleptic attacks, he regarded them as a more extensive radiation of inhibition throughout the cortex, spreading down the neuraxis through the thalamus and the hypothalamic areas. In all this he used the view of Pavlov [3] that sleep is internal inhibition diffused continuously over the cortex and descending also to lower parts of the brain.

Wilson's formulation of the phenomena seen in the narcoleptic patient as manifestations of varying degrees of radiation of internal inhibition (Pavlov) may be summarized as follows:

1. Trancelike states (catalepsy)
   (*a*) Partial spread of internal inhibition to the motor cortical area, producing a partial alteration of movement and plastic tone, or catatonia
   (*b*) No spread to cortical fields involving consciousness in the usual case
2. Cataplexy
   (*a*) Total spread of internal inhibition to the motor cortical area, producing total loss of movement and tone (which are

3. Pavlov, I. P.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated and edited by G. V. Anrep, London, Oxford University Press, 1927.

one and the same, according to Sherrington), or atonia, and consequent falling to the ground

(*b*) No spread to cortical fields involving consciousness

3. Sleep paralysis

(*a*) Total spread to the motor cortical area, producing atonia, as in cataplexy, but without falling, since the patient is in the sleeping position

(*b*) Spread of internal inhibition to the "edge of the cortical fields of consciousness," if such a term can be used, since this phenomenon occurs on the "edge" of sleep, whether incipient or emergent

4. Narcolepsy

(*a*) Spread of internal inhibition throughout the motor cortex and down the neuraxis to the levels of postural and viscerosympathetic control in the brain stem and the hypothalamus, leading to the pattern of motility of somatic and visceral muscle found in true sleep

(*b*) Spread of internal inhibition through the cortical and thalamic fields of consciousness, leading to the psychic phenomena of true sleep

Justification for the contention that the motor cortex is suspended or inhibited in activity during both sleep and cataplexy is found in the fact that plantar stimulation produces the pathologic sign of Babinski in both states. In sleep this phenomenon is well known, and Wilson [2] found it in cataplexy as well. The similarity of the cortical mechanism in true sleep and in narcoleptic sleep is given support by recent electroencephalographic studies. Cohn and Cruvant [4] found that the patterns of the brain waves in sleep and in the narcoleptic attack are similar in configuration, a fact which suggests the fundamental physiologic similarity in the cortex in the two states. What are the deficiencies in such a formulation? The following questions may be posed:

1. What is the peculiar quality of emotional stimuli which produces cataplexy?

2. What, as Wilson asks, is the ill understood reason that emotional stimuli should invariably cause inhibition of motility and tone in cataplectic attacks?

3. Can the apparently diverse phenomena of narcolepsy, cataplexy, sleep paralysis and catalepsy (trance) be kept in line in any elaboration made on the formulation?

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4. Cohn, R., and Cruvant, B. A.: Relation of Narcolepsy to the Epilepsies: A Clinical-Electroencephalographic Study, Arch. Neurol. & Psychiat. **51**:163 (Feb.) 1944.

4. What is it about the brain of the narcoleptic patient that makes it so susceptible to manifestations of inhibition?

THE "ULTRAPARADOXIC PHASE" OF PAVLOV

The second volume of translations of Pavlov's writings into English, "Conditioned Reflexes and Psychiatry," [5] contains many observations which are pertinent here, because they seem to throw light on the pathogenesis of narcolepsy. Pavlov found that the intensity of the conditioned reflexes of dogs depended on the intensity of the conditioned stimulus: A loud bell produces a greater food excitation than a faint one. This is true within certain ranges of the intensity of the conditioned stimulus, but beyond a critical maximal intensity variations of the effect may lead to certain pathologic phases of cortical activity: equivalent, in which strong and weak stimuli produce the same effect; paradoxic, in which weak stimuli give a greater response than the strong, or ultraparadoxic, in which excitatory conditioned stimuli become inhibitory and vice versa. These excessive stimuli, greater than those required to produce a maximal conditioned response, Pavlov called transmarginal or supramaximal, and these terms were translated by Gantt as ultramaximal. Thus, the law may be stated, according to Pavlov's observations, that ultramaximal conditioned stimuli may produce one of three pathologic phases in the cortex of the dog: equivalent, paradoxic or ultraparadoxic. In his introduction to Pavlov's work, Gantt [6] stated:

> . . . In dogs with a "weak nervous system" the above-described phases, particularly the ultraparadoxical, were prominent.

Pavlov [7] wrote:

> For every one of our animals (dogs) there is a maximum stimulus, a limit of harmless functional strain, beyond which begins the intervention of inhibition (the law of the limit of the intensity of stimulation). A stimulus, the intensity of which is beyond the maximum, instantly elicits inhibition, thus distorting the usual rule of the relationship between the magnitude of the effect and the intensity of excitation.

THE "ULTRAMAXIMAL STIMULUS" OF PAVLOV VERSUS THE "EMOTIONAL STIMULUS" OF THE NEUROLOGISTS IN THE PRODUCTION OF CATAPLEXY

The surprising feature of the case reported in the preceding article [8] is the infrequency of cataplectic attacks despite the magnitude and fre-

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5. Pavlov, I. P.: Lectures on Conditioned Reflexes, translated by W. H. Gantt, New York, International Publishers, 1941, vol. 2.

6. Pavlov,[5] p. 14.

7. Pavlov,[5] p. 51.

8. Fabing, H. D.: Narcolepsy: I. Combat Experience of a Soldier with Narcolepsy, Arch. Neurol. & Psychiat. **54**:367-371 (Nov.-Dec.) 1945.

quency of the emotion-laden situations which the soldier had to endure in combat. In addition, the case is a lesson. It illustrates that cataplexy does not occur in states of great emotional tension but that it is produced by sudden massive stimuli calling for massive response. How else can one explain the cataleptic attack produced in an experienced swimmer as a result of diving into water of comfortable temperature, such as occurred in this patient off Bizerte? The sudden massiveness of the cutaneous stimulus (water in contact with the entire surface of the skin) calling for a massive response immediately on rising to the surface (in swimming), and not any emotional quality in the act, produced cataplexy in this patient when he dived into water, both in premilitary and in military life.

Sudden laughter, analyzed physiologically, is the result of a massive instantaneous stimulus which calls for a total bodily reaction, and many have experienced the ultramarginal nature of it; with the resulting larval cataplectic phenomenon of motor weakness. In the vernacular of the theater there is a current phrase for it—a particularly funny comedy routine "lays the customers out in the aisles." The quick aiming of a gun has the same elements of a massive stimulus, requiring immediate massive motor response, and in my patient, as a consequence, it produced cataplexy whether he was aiming at a rabbit, at quail or at a man. The greatest single quality about baseball which makes it an excellent sport for participant and spectator alike is the split second stimulus-response reactions with which it is filled. These conditioned reflexes produced a sudden ultraparadoxic phase in my patient, with resultant cataplexy. His entire case history can be analyzed and every cataplectic attack can be explained on the basis of a sudden massive stimulus becoming ultramarginal, causing a perversion of the expected motor excitation into sudden motor inhibition. Conversely, the failure of cataplexy to occur in many emotion-charged situations, such as the explosion of shells nearby, is explained on the basis that the stimuli are not sudden enough in their impact on the central nervous system, and therefore not massive enough, to become ultramaximal. As the patient put it, "Shells never bothered me because I could hear them coming, and that way my nerves could get set for them."

It is probably true that no one has ever stopped to inquire into the nature of "emotional" stimuli causing cataplexy. One has reckoned only with their affective quality and has not noticed their intensity, whereas Pavlov taught that the emphasis should be the other way round. Because affect-laden stimuli are usually intense, the mistake is an easy one. Wilson suspected it when he wrote that "clinical data, however, prove that the matter of surprise has no little to do with cataplectic development." My patient's testimony was more eloquent in its sim-

plicity when he said: "It comes on when something big and sudden hits me . . . it's got to be big and fast, though, to knock me down."

One is now in a position to answer some of the questions posed earlier. First, what is the peculiar quality of emotional stimuli which produces cataplexy? The answer is that the peculiar quality is the intensity of the emotional stimulus, which in the narcoleptic person, susceptible as he is to excessive inhibition, becomes ultramaximal at lower than normal intensity. Second, what is the ill understood reason that emotional stimuli should invariably inhibit motility and tone in cataplectic attacks? In answer, emotional stimuli, being pathologically sudden and intense and therefore ultramaximal, according to Pavlov's law of the limit of the intensity of stimulation, produce the ultraparadoxic phase, with resultant massive inhibition in the motor cortex and consequent cataplectic fall.

PAVLOV'S CONCEPT OF INTERNAL INHIBITION, HYPNOSIS AND SLEEP

In the course of his studies on conditioned reflexes in dogs, Pavlov found that excitation could become perverted into inhibition not only by the application of a single massive ultramaximal stimulus but in a second way. When an excitatory stimulus of normal intensity is repeated again and again, there is an effect of summation, and this summation of small stimuli gradually transcends the margin, so that the law of the limit of the intensity of stimulation begins to operate once more and perverted states of cortical activity begin to become evident. When the ultraparadoxic phase is reached, previously excitatory stimuli, as they impinge on the cortex, become inhibitory. The internal inhibition thus generated differs from that produced by a single ultramaximal stimulus. In the case of a single ultramaximal stimulus immediate and transient inhibition occurs only in the cells directly involved, whereas in the case of summation of stimuli the slower development of inhibition is accompanied with a tendency of this neural state to spread across the cortex and down the neuraxis.

On the basis of these observations, together with many others on inhibition developed by other means, Pavlov came to the conclusion that natural sleep is merely a widespread process of internal inhibition, that it is generated by various means and that it may exhibit many hypnoidal manifestations before complete inhibition occurs. He was attracted to the further study of the phenomena "on the brink of sleep," which he found indistinguishable from hypnosis, and he found that many of these partially elaborated hypnoidal states of internal inhibition were analogous to symptoms of neuropsychiatric disorders in man. He wrote [7]:

> . . . We have seen already how an excitation of the same cell, lasting only a few minutes, lead toward the development in it of a process of inhibition, which

decreases its work and finally stops it altogether. . . . Inhibition, as already stated, has a tendency to spread, unless it meets with a counteraction in the conditions of a given environment. It expresses itself in phenomena of either partial or total sleep. Partial sleep is, evidently, the so-called *hypnosis.*

In discussing partial sleep further, he wrote [9]:

Irradiation of the inhibitory process of low tension is the condition known as hypnosis and is revealed in conditioned food reflexes by both components, the secretory and the motor. When inhibition (either differential or any other kind) arises under the above conditions, it most commonly causes peculiar conditions in the cerebral hemispheres. To begin with, contrary to the rule of a normally more or less parallel change in the magnitude of the salivary effect of conditioned food reflexes in accordance with the intensity of the stimuli, all the stimuli are equalised in their effect (the phase of equalisation). Further, weak stimuli produce more saliva than strong ones (paradoxical phase). And, lastly, a perversion of effects occurs: the positive conditioned reflex produces no effect whatever, whereas the negative conditioned reflex causes salivation (ultraparadoxical phase). The same is observed as regards the motor reaction; so, when a dog is offered food (*i. e.*, natural conditioned stimuli are put into action), it turns away from it, while when food is pushed or carried away the dog tries to reach it. Besides, it is sometimes possible to observe directly in the condition of hypnosis (in the case of conditioned food reflexes) a gradual spreading of inhibition over the motor region of the cortex. The first to be paralysed are the tongue and the muscles of mastication, after which the inhibition of the cervical muscles sets in, and, finally, that of all the muscles of the trunk. A further spreading of inhibition down the brain presents sometimes a state of catalepsy and finally manifests itself in heavy sleep.

Gantt [10] wrote of these experiments:

Also some of these dogs fell into a "hypnotic" state in which there was paralysis of the motor skeletal musculature, especially those muscles most concerned with the given excitation, *i.e.*, those of eating. Such animals stood like marble statues, drooling at the mouth but unable to take food. These Pavlov considered analogous to the patients, catatonics, who exhibit catalepsy and remain immobile to even painful stimuli, and consistently refuse food.

Thus it is seen that consequent on the spread of inhibition over the hemispheres many of the phenomena seen in the dog under experimental conditions are parallels of those seen in the narcoleptic patient. The cataleptic trance state and the sleep paralysis state of the patient are close to the partial sleep state of Pavlov's dogs, who were undergoing the effects of progressive spread of internal inhibition. It is evident, too, that the perverted phases of cortical activity, especially the ultraparadoxic, can arise in circumstances other than those produced by excessive or ultramaximal stimuli. That the summation of weak submaximal stimuli may, if applied repeatedly, produce inhibition by inducing the ultraparadoxic phase is an experience of everyday life. The slight (excitatory)

9. Pavlov,[5] p. 174.
10. Pavlov,[5] p. 14.

effect of rain on a tin roof quickly summates by repetition, becomes inhibitory and produces sleep. The same may be said for the stimulus of rocking a baby. Again, the objectivist who watches people in a railway carriage finds that the first part of the journey excites attention; but the summation of the sound of the clickety-click of the wheels, the endless whisking by of telegraph poles through the visual field and the sameness of green fields seen through the window soon produce partial sleep phenomena in most passengers. Facial muscles become masklike; eyes stare fixedly ahead; books and newspapers are held in an almost catatonic fashion in the hand. Then eyes close; the body sags; the book falls away, and one more traveler is asleep.

It appears that the narcoleptic patient differs from the normal person only because his excessive susceptibility to inhibition causes these phenomena to occur at pathologically low thresholds. Thus, repetitious stimuli of almost any kind quickly produced the ultraparadoxic phase, with consequent spreading inhibition, in the soldier whose case was described in the previous paper.[8] Any monotonous repeated stimulus, such as reading a magazine, sitting under a tree looking for squirrels or even the whizzing of shells overhead, produced narcoleptic sleep, or partial sleep, in him.

It is fair to state, therefore, in answer to the third question posed, that by pursuing Pavlov's theory of the spread of internal inhibition as the cause of these states, one may keep in line the apparently divergent phenomena of cataleptic trance, sleep paralysis and actual sleep in a formulation of the pathogenesis of narcolepsy. Furthermore, it is evident that these phenomena, like those of cataplexy, are pathologic not in kind but in degree, since larval manifestations are found in normal people. In cataleptic trance and in narcolepsy the spread of inhibition is slow and more generalized, whereas in cataplexy the inhibition is sudden and is confined to a group of motor cortical cells destined for excitation but perverted in their activity by a single excessive ultramaximal stimulus. In sleep paralysis the two types of inhibition (the slow generalized and the sudden isolated motor type) appear to be combined.

ABNORMAL SUSCEPTIBILITY OF THE BRAIN OF THE NARCOLEPTIC PATIENT TO INHIBITION

The pathologic basis of the narcolepsy-cataplexy syndrome, according to the foregoing formulation, resides in the abnormal susceptibility of the brain of the patient to inhibition. At the present time little is known of the nature of this process. The existence of inhibition as a fact of neurophysiology dates from the observation of the brothers Weber a century ago that stimulation of the peripheral end of the cut vagus nerve produces temporary cessation of the heart beat. Since

Sherrington's [11] observation, in 1893, that the knee jerk could be inhibited centrally, the phenomenon of inhibition in the central nervous system has been studied extensively. The concept of cortical inhibition is not confined to Pavlov. Among the more important contributions are those of Dusser de Barenne [12] and his colleagues, who studied the phenomenon of "extinction" in the exposed cortex, which Fulton [13] regards as identical with inhibition. Walshe,[14] in a recent analysis of the symptomatology of jacksonian epilepsy, showed the clinical application of spreading, contracting, changing states of inhibition in his cases. Pavlov,[15] however, seems to have been the only one to see an answer to the riddle of narcolepsy in this mechanism. Although he did not elaborate on his statement, he wrote:

> . . . To this mechanism [internal inhibition plus ultraparadoxical phase] one must, I think, refer many pathological symptoms, *e.g.*, narcolepsy, cataplexy, catalepsy, . . . catatonia, etc.

Although the fact of cortical inhibition does not appear to be in dispute, the nature of the phenomenon is not established. Gasser [16] stated:

> . . . The large number and the diversity of the theories about the nature of inhibition in the nervous system may be taken as a measure of the obscurity which has surrounded the subject. Some of the theories are hardly more than restatements in other terms of the fact that the neurons are inhibited. Others are fabricated in analogy with conditions making for unresponsiveness in other situations. A humoral agent is often postulated, but no such agent has been found; nor is there any evidence for two kinds of fibers, the excitatory and inhibitory, nor for two types of endings for one type of fiber. The Wedensky mechanism and anodal polarization are also not infrequently mentioned. In every instance, the suggestions can neither be accepted nor rejected.

With so little known about the normal process of central inhibition, it is improbable that any satisfying explanation of abnormal susceptibility to the process can be found at this time. Pavlov expressed the opinion that the answer to the fundamental nature of inhibition and its pathologic variations would come from the chemists. Suffice it to say

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11. Sherrington, C. S.: Note on the Knee-Jerk and the Correlation of Action of Antagonistic Muscles, Proc. Roy. Soc., London **52**:556-564, 1893.

12. Dusser de Barenne, J. G., and McCulloch, W. S.: Factors for Facilitation and Extinction in the Central Nervous System, J. Neurophysiol. **2**:319-355, 1939.

13. Fulton, J. F.: Physiology of the Nervous System, ed. 2, London, Oxford University Press, 1943.

14. Walshe, F. M. R.: On the Mode of Representation of Movements in the Motor Cortex, with Special Reference to "Convulsions Beginning Unilaterally" (Jackson), Brain **66**:104-139, 1943.

15. Pavlov,[5] p. 164.

16. Gasser, H. F.: The Control of Excitation in the Nervous System, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, vol. 32, pp. 169-193; cited by Fulton,[13] p. 85.

that the therapy applied today, with success in most cases, is the administration of excitant drugs—drugs which counteract inhibition—namely, ephedrine and amphetamine.

The answer to our last question, "What is it about the brain of the narcoleptic patient that makes it so susceptible to inhibition?" cannot be given. It can hardly be a static inherent property, for, according to Redlich,[17] the disorder does not ordinarily come on until after puberty. A tempting speculation arises if this last fact is considered with Pavlov's observation that the castration of dogs increases inhibition chronically. This suggests that the ultimate answer may prove to be an endocrine disorder, but such speculation requires study. The failure of autopsy material to aid in understanding the pathogenesis of the disorder is evidently due to the fact that it is a chemical disturbance unaccompanied with structural change.

SUMMARY

The case history of a soldier who began to have symptoms of narcolepsy, cataplexy and trancelike catalepsy in 1935 is reviewed. His condition was unrecognized, and he went through the Tunisian and Sicilian campaigns of World War II with his disease. Attacks of sleep occurred repeatedly throughout his combat career, but cataplectic spells were rare, only 2 instances being reported in nine months in the field. This absence of cataplectic episodes provoked inquiry into the pathogenesis of the disease, and it was found that cataplexy in man is the result not of an "emotional" stimulus but of an excessively strong, sudden stimulus, which causes a perversion of activity in cortical cells, so that a response destined to be excitatory becomes inhibitory. This explanation is found to be consistent with Pavlov's law of the limit of the intensity of stimulation, in which ultramaximal stimuli produce the ultraparadoxic phase in the cortex. Further inquiry into Pavlov's theory of sleep indicates that the phenomena of trancelike catalepsy, sleep paralysis and narcoleptic sleep are the result of the spread of inhibition across a brain more susceptible to this state than is the so-called normal brain.

CONCLUSIONS

On the basis of analysis of a case of narcolepsy in a combat soldier, a theory of the pathogenesis of narcolepsy, which is essentially an elaboration of the formulation of Wilson, is advanced.

1. The brain of the narcoleptic patient is regarded as having an abnormal susceptibility to inhibition, and it is held that this is the fundamental pathophysiologic cause of the disorder.

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17. Redlich, E.: Epilegomena zur Narkolepsiefrage, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:128-173, 1932.

2. The nature of the process of inhibition in the central nervous system is unknown, and the cause of the abnormal susceptibility of the narcoleptic patient to this process is equally obscure.

3. It is held that Pavlov's law of the limit of the intensity of stimulation is applicable to the narcoleptic patient. This law states that when a single stimulus or the summated effect of repeated stimuli becomes too strong for the capacity of cortical cells the ultraparadoxic phase of cortical activity supervenes, in which excitatory stimuli become inhibitory.

4. In conformity with this law, it is held that the phenomenon of cataplexy results from a single excessive ultramaximal stimulus, the magnitude of which is such that it produces the ultraparadoxic phase and consequent sudden internal inhibition in motor cortical cells which were destined for excitation. This sudden inhibition in these cells causes loss of tone and falling to the ground. In cataplexy it is held that there is no spread of internal inhibition to cortical fields involving consciousness.

5. The case of the combat soldier described here is used to illustrate the fact that it is not the effective quality but, rather, the magnitude of so-called emotional stimuli which provokes the phenomenon.

6. The trancelike cataleptic states seen in narcoleptic patients are held to be due to the summation of repeated stimuli provoking the ultraparadoxic phase, with partial spread of internal inhibition to the motor cortical area, producing a partial alteration of movement and plastic tone, or catatonia, without spread to the cortical fields involving consciousness in the usual case.

7. The phenomenon of sleep paralysis sometimes seen in narcoleptic attacks is held to be similar to that of cataplexy, but the patient does not fall because he is in the sleeping position at the time. It is held that in sleep paralysis there is partial spread of generalized inhibition together with sudden isolated inhibition in motor cortical cells.

8. The narcoleptic attack itself is held to be due to the effect of the summation of repeated stimuli, which produce the ultraparadoxic phase, and consequent massive internal inhibition, which spreads widely over the cortex and subcortical centers as well, leading to both the motor and the psychic phenomena of sleep.

9. The failure of autopsy material to shed light on this disorder is explained on the basis that abnormal susceptibility to inhibition is probably a chemical disturbance without demonstrable structural change.

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DISTURBANCES IN SLEEP MECHANISM: A CLINICOPATHOLOGIC STUDY

V. Anatomic and Neurophysiologic Considerations

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ANATOMIC CONSIDERATIONS

FROM the analysis of the material in our previous communications,[1] the cases reported in the literature and the results of animal experimentation, it is possible partly to reconstruct the anatomic centers and their connections regulating the sleeping mechanism.

The available data suggest that certain cortical areas, namely, the frontal, premotor, motor, temporal, cingular and hippocampal (as illustrated by the cases in our presentations[1]; the cases in Righetti's[2] collection, and the cases reported by Léchelle, Alajouanine and Thévenard,[3] Kolodny,[4] Frazier[5] and others) may act as centers in the integration of hypersomnia and insomnia (figure). The ability of man to fall asleep voluntarily suggests that this mechanism is controlled by

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1. Davison, C., and Demuth, E. L.: Disturbances in Sleep Mechanism: A Clinicopathologic Study. (*a*) I. Lesions at the Cortical Level, Arch. Neurol. & Psychiat. **53**:399 (June) 1945; (*b*) II. Lesions at the Corticodiencephalic Level, ibid. **53**:241 (Oct.) 1945; (*c*) III. Lesions at the Diencephalic Level (Hypothalamus), ibid. **55**:111 (Feb.) 1946; (*d*) IV. Lesions at the Mesencephalo-Metencephalic Level, ibid. **55**:126 (Feb.) 1946.

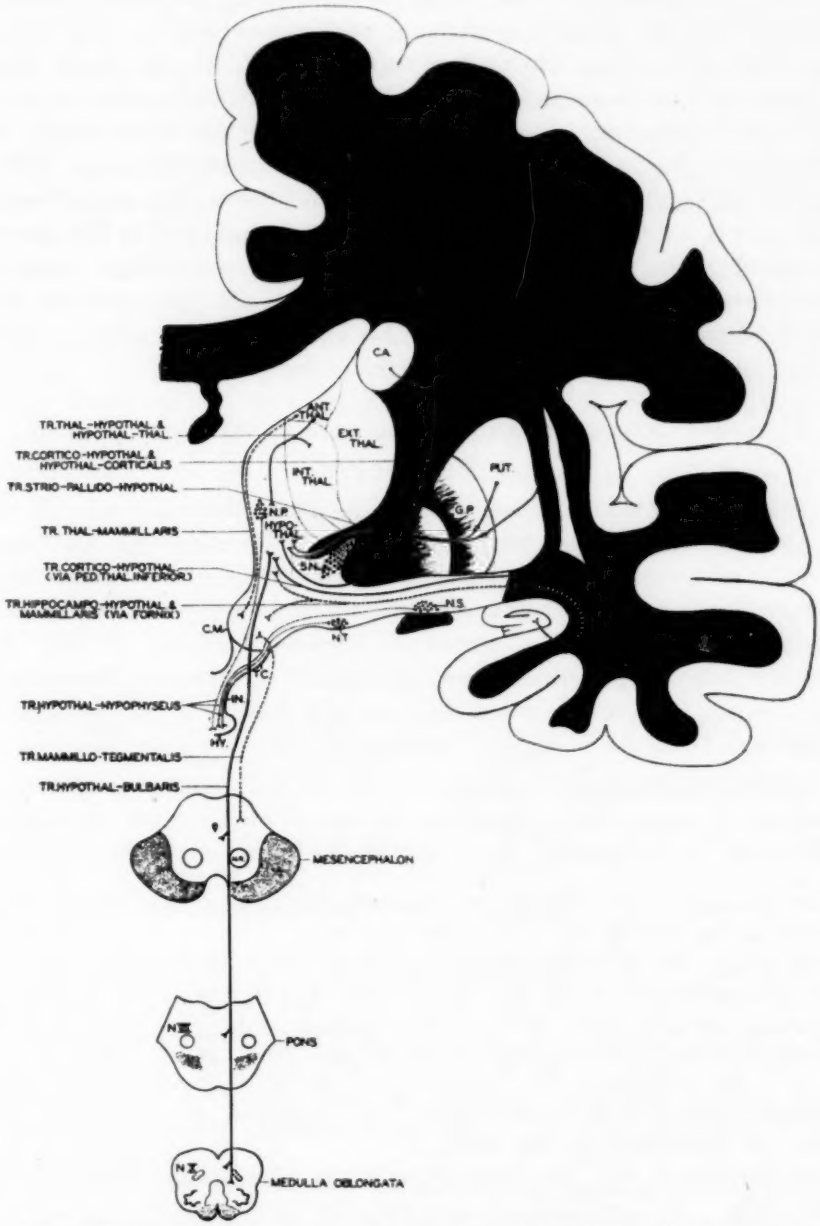
2. Righetti, R.: Contributo clinico e anatomopatologica allo studio dei gliomi cerebrali e all'anatomia delle vie ottiche centrali, Riv. di pat. nerv. **8**:241 and 289, 1903.

3. Léchelle; Alajouanine, and Thévenard: Deux cas de tumeur du lobe frontal à forme somnolente, Bull. et mém. Soc. med. d. hôp. de Paris **49**:1347, 1925.

4. Kolodny, A.: The Symptomatology of Tumours of the Temporal Lobe, Brain **51**:385, 1928.

5. Frazier, C. H.: Tumor Involving the Frontal Lobe Alone, Arch. Neurol. & Psychiat. **35**:525 (March) 1936.

the higher cortical centers. Bard's [6] experiments on sham rage furnished further indications that the hypothalamus is to some extent under the



Anatomic connections of the cerebral cortex with centers of the brain stem.

6. Bard, P.: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928.

control of the cerebral cortex. Sleep impulses, as in affective states for the expression of emotion and feelings (Davison and Kelman [7] and others), are mediated by voluntary and involuntary pathways, probably controlled by the corticohypothalamic pathways (figure). The voluntary efferent impulses are probably mediated via the pyramidal tract. Spiegel [8] and his associates assumed that corticofugal impulses to autonomic structures may be conducted at least partly by fibers joining the pyramidal system and partly by extrapyramidal fibers from areas 3, 4, 5 and 6. Although, according to Spiegel,[8] direct fibers from areas 3 and 5 could not be traced to the hypothalamus, this should not be interpreted as meaning that extrapyramidal conduction of corticofugal impulses from these areas to the hypothalamus does not exist. It is possible that the hypothalamus may be reached by extrapyramidal systems using unmyelinated fibers or intercalated relay stations.

PROBABLE AFFERENT AND EFFERENT CONNECTIONS OF THE HYPOTHALAMUS

Medial Forebrain Bundle (figure).—This pathway, part of the hippocampohypothalamic tract, consisting of unmyelinated and myelinated fibers, runs between the ventromedial olfactory correlation areas of the cortex and the preoptic and hypothalamic areas and carries both ascending and descending impulses (Ariëns Kappers, Huber and Crosby [9]; Gurdjian [10]; Roussy and Mosinger [11]; Fulton and Ingraham,[12] and others). There is a possibility that this bundle is also in intimate connection with the striatum (caudate nucleus and putamen).

Corticohypothalamic Pathways.—The cortical control of the hypothalamus is most likely mediated through indirect fiber connection from areas 3, 4, 5 and 6. The only known direct corticohypothalamic

7. Davison, C., and Kelman, H.: Pathological Laughing and Crying, Arch. Neurol. & Psychiat. **42**:595 (Oct.) 1939.

8. Spiegel, E. A.: Bemerkungen zur Theorie des Bewusstseins und zum Schlafproblem, Ztschr. f. d. ges. exper. Med. **55**:183, 1927; Die Zentren des autonomen Nervensystems, Berlin, Julius Springer, 1928; The Centers of the Vegetative Nervous System, Bull. Johns Hopkins Hosp. **50**:237, 1932.

9. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936.

10. Gurdjian, E. S.: The Diencephalon of the Albino Rat, J. Comp. Neurol. **43**:1, 1927.

11. Roussy, G., and Mosinger, M.: Étude anatomique et physiologique de l'hypothalamus, Rev. neurol. **1**:848, 1934; L'hypothalamus chez l'homme et chez le chien, ibid. **63**:1, 1935.

12. Fulton, J. F., and Ingraham, F. D.: Emotional Disturbances Following Experimental Lesions of the Base of the Brain (Prechiasmal), J. Physiol. **67**: xxvii, 1929.

connections, however, are those of the fornix and certain olfactory systems.

The fornix, or the hippocampohypothalamic tract (figure), arising in the hippocampus, is a direct corticohypothalamic pathway. As is well known, this pathway contains corticoseptal, corticohabenular and corticohypothalamic fibers. The fibers, as demonstrated by Edinger and Wallenberg,[13] end in the medial and lateral mamillary nuclei and in the rostral portion of the tuber adjacent to these nuclei (figure). Papez[14] stated that the fornix is an important link in a circuit controlling the mechanism of emotion.

Roussy and Mosinger[11] expressed the belief that fibers from the temporal lobe via the inferior thalamic peduncle (figure) reach the nucleus supraopticus and the anterior hypothalamic area. They also mentioned an internal corticohypothalamic fasciculus. Greving[15] suggested the existence of a frontotuberal tract. Krieg[16] postulated a medial corticohypothalamic tract arising in the hippocampus. Nicolesco and Nicolesco[17] stated the belief that cortical fibers reach the hypothalamus via the inferior thalamic peduncle and other paths of the forebrain.

The existence of indirect excitatory (Karplus and Kreidl[18]) and inhibitory (Bard,[19] Bard and Rioch[20]) pathways seems to be accepted by many reliable observers (Clark and associates,[21] Ranson and Magoun[22] and others). There also is some evidence for a septohypothalamic pathway, partly by way of the medial forebrain bundle. Wallenberg,[23]

13. Edinger, L., and Wallenberg, A.: Untersuchungen über den Fornix und das Corpus mammillare, Arch. f. Psychiat. **35**:1, 1902.

14. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

15. Greving, R., in von Moellendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927.

16. Krieg, W. J. S.: The Hypothalamus of the Albino Rat, J. Comp. Neurol. **55**:19. 1932.

17. Nicolesco, I., and Nicolesco, M.: Quelques données sur les centres végétatifs de la région infundibulo—tubérienne et de la frontière diencéphalo-télencéphalique, Rev. neurol. **36**:289, 1939.

18. Karplus, J. P., and Kreidl, A.: Gehrin und Sympathicus: II. Ein sympathicus-zentrum in Zwischenhirn, Arch. f. d. ges. Physiol. **135**:401, 1910.

19. Bard, P.: The Central Representation of the Sympathetic Nervous System as Indicated by Certain Physiological Findings, A. Research Nerv. & Ment. Dis., Proc. **9**:67-91, 1930.

20. Bard, P., and Rioch, D. M.: A Study of Four Cats Deprived of Neocortex and Additional Portions of the Forebrain, Bull. Johns Hopkins Hosp. **60**:73, 1937.

21. Clark, W. E. L.; Beattie, J.; Riddoch, G., and Dott, N. M.: The Hypothalamus, Edinburgh, Oliver & Boyd, 1938.

22. Ranson, S. W., and Magoun, H. W.: The Hypothalamus, Ergebn. d. Physiol. **41**:56, 1939.

23. Wallenberg, A.: Bemerkenswerte Endstätten der Grosshirnfaserung bei Säugern, Jahrb. f. Psychiat. u. Neurol. **51**:295, 1934.

following frontal lesions in guinea pigs, demonstrated a degenerated neocorticoseptal tract. Mettler [24] also showed such a pathway by Marchi preparations in the monkey. Clark and associates [21] suggested the existence of a pathway from the frontal lobe to the hypothalamus, with a relay in the zona incerta. Possible relays via the dorsal thalamus from the frontal lobe have also been indicated by Clark and associates,[21] Mettler [24] and Levin.[25] Our cases of corticodiencephalic lesions [1b] and the reports of other authors also suggest the possibility of such a pathway. These cases seem to indicate that the cortex controls the main sleeping center, the hypothalamus, either in an excitatory or in an inhibitory manner.

Hypothalamocortical Connections.—Such pathways have not been demonstrated, but their existence is probable.

DIENCEPHALIC AND STRIOPALLIDAL CONNECTIONS

The importance of the hypothalamus, and possibly of other diencephalic structures, in the regulation of sleep has been amply illustrated clinically and experimentally. We cannot but strongly emphasize that in many of the clinical cases, including some of our own, the lesions were widespread and postulation of localization on that basis alone should be made with reservations, because areas adjacent to the hypothalamus may also be implicated by compression or edema.

Thalamohypothalamic and Hypothalamothalamic Pathways (figure) —These pathways need not be discussed in detail, for the evidence of their existence is generally accepted (Clark and associates,[21] Walker,[26] Crouch and Thompson,[27] Greving [15] and others). Many of the fibers are myelinated. Whether these pathways are afferent or efferent systems has not been solved. Briefly, it can be stated that they consist of fibers passing from the medial and midline thalamic nuclei to the hypothalamic nuclei (figure). There are also probable connections via the inferior thalamic peduncle with the rostral hypothalamic and the lateral tuberal nuclei. In human material, Ingram [28] demonstrated fibers from the anterior part of the thalamus which run ventrally into the medial and lateral preoptic areas. Some of these fibers may belong

24. Mettler, F. A.: Corticofugal Fiber Connections of the Cortex of Macaca Mulatta: The Frontal Region, J. Comp. Neurol. **61**:509, 1935.

25. Levin, P. M.: The Efferent Fibers of the Frontal Lobe of the Monkey, Macaca Mulatta, J. Comp. Neurol. **63**:369, 1936.

26. Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938.

27. Crouch, R. L., and Thompson, J. K.: The Afferent Fibers of the Thalamus of Macacus Rhesus, J. Comp. Neurol. **69**:255 and 449, 1938.

28. Ingram, W. R.: Nuclear Organization and Chief Connections of the Primate Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:193, 1940.

to the stria terminalis. Farther caudally, fibers appear to swing ventromedially out of the inferior thalamic peduncle into the lateral and anterior hypothalamic regions. Many fibers from the substantia innominata enter the lateral preoptic and hypothalamic areas dorsal to the supraoptic nucleus. Some fibers from the substantia innominata enter the supraoptic nucleus, turn dorsalward and join the inferior thalamic peduncle, but there is no conclusive evidence that these fibers end in the supraoptic nucleus.

Thalamomamillary and Mamillothalamic Fibers.—Thalamomamillary connections have been demonstrated in lower forms. These fibers set up relays of somatic, visceral and sensory impulses from the neopallium to the hypothalamus. The impulses from the hypothalamus to the thalamus are mediated via the (1) mamillothalamic tract (figure), the origin and connections of which are well known and (2) more diffuse and less well defined connections passing through the periventricular system. The mamillothalamic tract most likely serves as a link between the hypothalamus and the cerebral cortex, especially the gyrus cingulus. Some of the less well defined and diffuse connections belong to the inferior thalamic peduncle, while most of the others lie fairly close to the wall of the ventricle.

Stria Terminalis.—This also contains preoptic and hypothalamic components, which convey fibers from the amygdaloid nucleus to these regions. Ariëns Kappers and his associates [9] expressed the belief that fibers of the stria terminalis are distributed to all major hypothalamic areas as far as the perimamillary area, except for the periventricular system and the nucleus suprachiasmaticus, the nucleus paraventricularis and the nucleus supraopticus. Roussy and Mosinger [11] and Clark [21] mentioned connections of the stria terminalis with practically all the hypothalamic nuclei. In man, Ingram [28] observed fibers of the stria terminalis stream ventrally toward the preoptic and hypothalamic areas, some crossing beneath the anterior commissure.

Supraoptic Commissures.—These fibers and their relationship to the hypothalamus as afferent systems concerned in the integration of emotional expressions have been emphasized by Papez.[14] On the basis of experimental studies in cats, Ingram [28] and his associates stated that they were uncertain whether the specific functions of these commissures had yet been solved.

Striopallidohypothalamic and Subthalamohypothalamic Fibers.—Such connections have been reported by many observers, but the evidence is not conclusive. The secondary involvement of the striatum, pallidum and subthalamic nuclei in many of the clinicopathologic cases and the edema of these structures which must have occurred in the experimental animals suggest that these areas are in intimate connec-

tions with the hypothalamus (figure). Interruption of these pathways on their way to the hypothalamus may lead to disturbances in the sleep mechanism.

EFFERENT SYSTEM

The efferent pathways of this system consist of the following tracts:

1. Mamillothalamic tracts.

2. Mamillotegmental tract.

3. Periventricular system and dorsal longitudinal fasciculus. These pathways possibly arise throughout the hypothalamus but come mainly from the posterior hypothalamic area. They descend through the central gray matter of the aqueduct, with probable contributions to the tectal and tegmental nuclei (figure).

4. Diffuse descending connections. These are caudal continuations of the medial forebrain bundle. Physiologic experiments indicate that these fibers are scattered in the lateral portions of the tegmentum and conduct hypothalamic impulses to the lower sympathetic centers.

5. Hypothalamohypophysial pathways (figure). This well known tract runs from the supraoptic, paraventricular and tuberal nuclei to the neurohypophysis by way of the neural stalk.

6. Intrahypothalamic pathways. Of these connections between the various hypothalamic nuclei, the best demonstrated one is that composed of paraventriculosupraoptic and paraventriculotuberal fibers, with unknown destination.

7. Fasciculus residualis of Marie and Léri.[29] These fibers descend along the optic tract to enter the supraoptic nucleus. The fasciculus residualis may belong to the ansa lenticularis.

MESENCEPHALOMETENCEPHALOHYPOTHALAMIC SYSTEM

Mamillary Peduncle.—Papez [14] and Rundles and Papez [30] considered this structure as one of the important afferent paths of the hypothalamus. Papez [14] suggested that this tract originates from the ventral part of the midbrain and from the substantia nigra. He stated the opinion that the substantia nigra, with the medial lemniscus, exercises a dynamic influence on the mamillary body and the mechanism for maintaining general consciousness. Ingram [28] expressed the opinion that the mamillary peduncle in man is not very conspicuous and that it is an ascending

29. Marie, P., and Léri, A.: Persistance d'un faisceau intact dans les bandelettes optiques après atrophie complète des nerfs: Le faisceau résiduaire de la bandellete; le ganglion optique basal et ses connexions, Rev. neurol. **13**:492, 1905.

30. Rundles, R. W., and Papez, J. W.: Connections Between the Striatum and the Substantia Nigra in a Human Brain, Arch. Neurol. & Psychiat. **38**:550 (Sept.) 1937.

system of mesencephalic origin, ending mostly in the lateral mamillary nucleus. He expressed doubt as to whether it contains fibers from the substantia nigra or whether it forms a relay in the lemniscal system.

Mamillotegmental Tract.—This is the efferent tract, most likely arising from the dorsal part of the medial mamillary nucleus and terminating in the dorsal tegmental nucleus of the midbrain (figure). In man, the mamillotegmental tract mingles with descending fibers from other parts of the hypothalamus as it passes into the capsule of the red nucleus.

Other Connections.—Another afferent connection, demonstrated only physiologically, is the possible vagosupraoptic system (Chang and associates [31]; Huang [32]; Bronk, Lewy and Larrabee.[33]

NEUROPHYSIOLOGIC CONSIDERATIONS

THEORIES OF SLEEP

Numerous theories of sleep have been suggested, and it will be impossible in this presentation to do all of them justice. The less important theories will only be mentioned briefly.

Humoral Theory.—According to some observers, end products of metabolism are accumulated in tissues or in certain organs, resulting in circulatory changes and the induction of sleep. The gradual removal of these substances during sleep leads to a return of the waking state. Experimental evidence so far has not shown differences in the blood flow in animals during sleep and during wakefulness (Gibbs, Gibbs and Lennox [34]). Another humoral theory is the endocrine, according to which the hypophysis controls the sleep mechanism.

Vegetative, or Sympathetic-parasympathetic Theory (Hess [35] and others).—According to Hess,[35] sleep is a parasympathetic function, while waking is the result of action of the sympathetic system.

Neural or Dendritic Theories.—The main theory of this type states that the dendrites of the cortical cells are retracted by ameboid movements, thus breaking the contact with neighboring neurons and resulting

31. Chang, H. C.; Hsieh, W. M.; Li, T. H., and Lim, R. K. S.: Humoral Transmission of Nerve Impulses at Central Synapses: IV. Liberation of Acetylcholine into the Cerebrospinal Fluid by Afferent Vagus, Chinese J. Physiol. **13**: 153, 1938.

32. Huang, J. J.: A Vagus-Post-Pituitary Reflex: IV. On the Determination of Its Pathways with a Comment on the Hypothalamic Sympathetic Mechanism, Chinese J. Physiol. **13**:367, 1938.

33. Bronk, D. W.; Lewy, F. H., and Larrabee, M. G.: The Hypothalamic Control of Sympathetic Rhythms, Am. J. Physiol. **116**:15, 1936.

34. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow During Sleep in Man, Brain **58**:44, 1935.

35. Hess, W. R.: Der Schlaf, Klin. Wchnschr. **12**:129, 1933.

in sleep. Powerful impulses leading to elongation of the dendrites reestablish the broken contacts and result in awakening.

Inhibition Theories.—Of inhibition theories advocated by several investigators, the only one discussed here is that proposed by Pavlov.[36] According to this investigator,[36] sleep is the result of a widespread cortical inhibition. Inhibition is the decrease in activity of one part of an organ as a result of excitation or increased activity elsewhere. Pavlov stated the belief that sleep is nothing but internal inhibition which is widely radiated, extending over the whole mass of the cerebral hemispheres and involving the lower centers of the brain as well. The inhibition thus can not only affect the entire cerebral cortex but can extend to subcortical areas. This widespread radiation of cortical inhibition is a result of conditioned stimuli, the repeated application of which leads to sleep. Experimental observations by others (Liddell, Anderson and James [37]) failed to support the summation and radiation theories of internal inhibition.

Narcoleptic sleep, according to Wilson,[38] cannot be explained on the basis of this theory, for the patient sometimes is asleep on his feet while walking, marching or on horseback—a state which cannot be identified with cortical inhibition alone. Pavlov's theory underrates the comparative anatomy of the diencephalic center, the existence of which experimental and clinicopathologic studies confirm.

Corticodiencephalic and Diencephalic Theories (Purkinje and associates,[39] Mauthner,[40] Kleitman [41] and others).—The corticodiencephalic, or evolutionary, theory presupposes that for the initiation of sleep there is an interruption of the afferent pathways to the cerebral cortex. As a result of pathologic changes in the ventricular gray matter (Mauthner [40]), there occurs a break in the conducting pathways to and from the cerebral cortex. Afferent stimulation does not reach consciousness, and efferent impulses do not reach the hypothalamus because of a break in conduction in the central gray matter despite the fact that the sensory and motor cortex may be intact. There is suggestive experi-

36. Pavlov, I. P.: The Identity of Inhibition with Sleep and Hypnosis, Scient. Monthly **17**:603, 1923: Innere Hemmung der bedingten Reize und der Schlaf, ein und derselbe Prozess, Skandinav. Arch. f. Physiol. **44**:42, 1923.

37. Liddell, H. S.; Anderson, O. D., and James, W. T.: An Examination of Pavlov's Theory of Internal Inhibition, Am. J. Physiol. **90**:430, 1929.

38. Wilson, S. A. K.: The Narcolepsies, Brain **51**:63, 1928.

39. Purkinje, J. E.: Wachen, Schlaf, Traum und verwandte Zustände, in Wagner, R.: Handwörterbuch der Physiologie, Brunschweig, F. Vieweg u. Sohn, 1846, vol. 3, p. 412.

40. Mauthner, L.: Pathologie und Physiologie des Schlafes, Wien. klin. Wchnschr. **3**:445, 1890.

41. Kleitman, N.: Sleep and Wakefulness as Alternating Phases in the Cycle of Existence, Chicago, University of Chicago Press, 1939.

mental evidence (Bremer [42] and Adrian [43]) that in normal sleep the cortex becomes deafferented, and, therefore, that sleep is impossible without the cortex. According to this theory, wakefulness is a subcortical, most likely a hypothalamic, function, whereas forced wakefulness and diurnal sleep are cortical functions. Ranson [44] called forced wakefulness, or wakefulness of necessity, a hypothalamic drive. The failure to keep the center for wakefulness (hypothalamus) in a state of continued excitation causes a return to the condition of sleep. At this point it may be advisable to review briefly the experimental data showing the important role that the diencephalic centers, especially the hypothalamus, play in the regulation of the sleep function. For the data regarding the influence of the cerebral cortex on sleep or wakefulness, the reader is referred to the discussion in previous publications [1] on lesions at the cortical and corticodiencephalic levels.

PHYSIOLOGIC EVIDENCE

Experimental Lesions.—Experimental lesions in the region of the hypothalamus are variable and numerous. Most of the experiments (Marinesco, Sager and Kreindler [45]; Ito [46]; Ranson and Ingram,[47] and Barris and Ingram [48]), especially those by Ranson and his co-workers, which were controlled very carefully, prove that the hypothalamus is concerned with the mechanism of sleep. Ranson [49] and his associates found that damage to the posterior part of the lateral hypothalamic area bilaterally produced somnolence. Somnolence could be induced in animals in which the central gray matter around the aqueduct was spared, and it was not present in some animals with lesions of the central gray matter around the aqueduct. Destruction of the anterior part of the lateral hypothalamus was less effective in producing somnolence than destruction of the posterior part. In 7 monkeys large bilateral lesions in the thalamus did not produce somnolence. Ranson [49] con-

42. Bremer, F.: Cerveau "isolé" et physiologie du sommeil, Compt. rend. Soc. de biol. **118**:1235, 1935.

43. Adrian, E. D.: The Physiology of Sleep, Lancet **1**:1296, 1937.

44. Ranson, S. W.: The Hypothalamus, Tr. & Stud., Coll. Physicians, Philadelphia **2**:222, 1934; Sleep, Scient. Monthly **38**:473, 1934.

45. Marinesco, G.; Sager, O., and Kreindler, A.: Recherches expérimentales sur le mécanisme du sommeil, Bull. Acad. de méd., Paris **100**:752, 1928.

46. Ito, S.: Das Tuber cinereum und der Schlaf, Fukuoka-Ikwadaigaku-Zasshi **24**:35, 1931; abstracted, Ber. ü. d. ges. Physiol. u. exper. Pharmakol. **64**:156, 1932.

47. Ranson, S. W., and Ingram, W. R.: Catalepsy Caused by Lesions Between the Mammillary Bodies and Third Nerve in the Cat, Am. J. Physiol. **101**:690, 1932.

48. Barris, R. W., and Ingram, W. R.: The Effect of Experimental Hypothalamic Lesions upon Blood Sugar, Am. J. Physiol. **114**:555, 1936.

49. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

cluded that the posterior part of the lateral hypothalamic area is the center for integration of emotional expression and suggested that it be termed a waking center. When it is thrown out of function, somnolence ensues. Harrison [50] (1940), by placing bilateral electrolytic lesions in the lateral hypothalamic area, produced somnolence. Clinically, in most of our cases of somnolence with lesions of the diencephalon the posterior and lateral parts of the hypothalamus were involved. Because other parts of the hypothalamus were also involved, it would be impossible, on a clinicopathologic basis, to state definitely that only the posterolateral part of the hypothalamus is concerned with somnolence.

Electrical Stimulation.—Electrical stimulation of the diencephalon in animals was carried out by Marinesco and associates [45]; Ito [46]; Hess [35]; Mussen [51]; Kabat, Anson, Magoun and Ranson [52]; Wassermann,[53] and and Harrison.[50] In none of these experiments was sleep produced, but most observers elicited evidences of excitement. White [54] found that in man mechanical and electrical stimulation of the hypothalamus produced bradycardia, a rise in blood pressure and a tendency to drowsiness or coma. Hess [35] was the only one who induced sleep by stimulation of structures in the brain stem. His results were accepted by many observers (von Economo,[55] Ebbecke,[56] Adie,[57] Trömner [58] and others) as proving Pavlov's [36] contention that sleep is an active inhibition of the cortex. Hess's [35] experiments were justifiably criticized by Harrison, Magoun and Ranson,[59] who repeated the experiment.

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50. Harrison, F.: An Attempt to Produce Sleep by Diencephalic Stimulation, J. Neurophysiol. **3**:156, 1940; Hypothalamus and Sleep, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:635, 1940.

51. Mussen, A. T.: Cerebellum and Red Nucleus, Arch. Neurol. & Psychiat. **31**:110 (Jan.) 1934.

52. Kabat, H.; Anson, B. J.; Magoun, H. W., and Ranson, S. W.: Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastro-Intestinal Motility, Am. J. Physiol. **112**:214, 1935.

53. Wassermann, M.: Prispevik, therapii nespavosti, Časop. lék. česk. **63**: 273, 1924; abstracted, Med. Klin. **20**:1018, 1924.

54. White, J. C.: Autonomic Discharge from Stimulation of the Hypothalamus in Man, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:854, 1940.

55. von Economo, C.: Ueber den Schlaf, Wien. klin. Wchnschr. (supp.) **38**:1, 1926; Studien über den Schlaf, Wien. med. Wchnschr. **76**:91, 1926; Schlaftheorie, Ergebn. d. Physiol. **28**:312, 1929.

56. Ebbecke, U.: Physiologie des Schlafes, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 17, p. 563.

57. Adie, W. J.: Idiopathic Narcolepsy: A Disease Sui Generis, with Remarks on the Mechanism of Sleep, Brain **49**:257, 1926.

58. Trömner, E.: Funktion und Lokalization des Schlafes, Arch. f. Psychiat. **86**:184, 1929.

They showed that sleep was easily obtained by passage of the current through the lateral hypothalamic area, but only when such stimulation was associated with corresponding lesions. Many animals which gave evidence of excitement and did not go to sleep showed no lesions microscopically. In many animals with sleep disturbances the lesions were small and could easily have been overlooked by a method of localization such as the vertical projection technic used by Hess.[35] Harrison [59] also produced somnolence in several animals by passing a steady direct current through the lateral hypothalamic area; lesions were present in these animals. Gagel [60] noticed sleep and unconsciousness in 14 cases in which the caudal part of the hypothalamus was mechanically stimulated at operation. He stated the belief that the caudal part of the hypothalamus is inhibitory to the cortex, whereas the oral part is excitatory. Damage to the oral part, according to Gagel,[60] results in decreased cortical activity. The consensus seems to be that when sleep is caused by passage of an electric current it is the destructive effects of the current and not the stimulating factors which are responsible for the somnolence.

PHARMACOLOGIC EVIDENCE

Barbiturates.—Some observers concluded that the hypothalamus was the sleep center because they demonstrated a selective concentration of barbiturates in the hypothalamus during narcosis (Sahlgren,[61] Lafora and Sanz [62]), while others indicated that barbiturates are present in high concentration in the hypothalamus during anesthesia (Keeser and Keeser [63]). These assumptions have been refuted by Koppanyi, Dille and Krop [64] and others.

Sympathomimetic and Parasympathomimetic Drugs and Their Antagonists.—Cannon's [65] concept of the parasympathetic system as

59. Harrison, F.; Magoun, H. W., and Ranson, S. W.: Some Determinations of Thresholds to Stimulation with the Faradic and Direct Current in the Brain Stem, Am. J. Physiol. **121**:708, 1938.

60. Gagel, O.: Symptomatologie der Erkrankungen des Hypothalamus, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 5, p. 482.

61. Sahlgren, E.: Experimentelle Untersuchungen über den Angriffspunkt des Luminals im Gehirn bei Kaninchen, Acta psychiat. et neurol. **9**:129, 1934.

62. Lafora, G. R., and Sanz, J.: Sul sonno sperimentale prodotto da una azione su la regione del diencefalo e del III ventricolo, Cervello **11**:86, 1932.

63. Keeser, E., and Keeser, J.: Ueber die Lokalisation des Veronals, der Phenyläthyl- und Diallylbarbitursaüre im Gehirn, Arch. f. exper. Path. u. Pharmakol. **125**:251, 1927.

64. Koppanyi, T.; Dille, J. M., and Krop, A.: Studies on Barbiturates: VII. Distribution of Barbiturates in The Brain, J. Pharmacol. & Exper. Therap. **52**:121, 1935.

65. Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-Effector Systems, New York, The Macmillan Company, 1937.

preserving the bodily reserves suggested to some observers that sleep is essentially a parasympathetic integration. As is well known, during normal sleep various divisions of the parasympathetic outflow are active. This is manifested by constriction of the pupils, slowness in heart action and retardation of the oxidation processes in the body as a whole. Some investigators have attempted to produce sleep with drugs known to stimulate structures innervated by the sympathetic nervous system. Marinesco, Sager and Kreindler,[66] on the basis of the production of a delayed sleeplike state in animals by the intraventricular injection of choline, a parasympathetic stimulant, suggested the possibility of a parasympathetic dominance during sleep. Dikshit,[67] by injecting acetylcholine into the lateral ventricles or directly into the hypothalamic region in cats, produced a condition closely resembling sleep. Henderson and Wilson,[68] however, were unable to produce sleep in most of their patients. In these subjects the slight effects of the acetylcholine were abolished by atropine. It was therefore concluded that the action of acetylcholine is central and that there is no conclusive evidence that acetylcholine or choline can produce sleep by central stimulation of parasympathetic centers. Harrison [50]; Hess [69]; Marinesco, Sager and Kreindler,[66] and Lafora and Sanz [62] produced sleep with intraventricular injections of ergotamine. They expressed the belief that this action was due to a depression of the central sympathetic centers, with dominance of the parasympathetic system. The effect of ephedrine, which alleviates somnolence in cases of narcolepsy, was thought to indicate that the drug increases the activity of the central sympathetic centers. Ranson and Magoun [22] concluded that the parasympathetic dominance was probably due to decreased sympathetic, and not to parasympathetic, activity. So far there is insufficient evidence that sleep is the result of increased parasympathetic activity.

Chemical Stimulation.—Metallic Ions: It is known that an increase in the concentration of ionic calcium causes a decrease in the irritability of neural tissue, whereas an increase in the concentration of ionic potassium increases the irritability. Demole [70] and Cloëtta and

66. Marinesco, G.; Sager, O., and Kreindler, A.: Experimentelle Untersuchungen zum Problem des Schlafmechanismus, Ztschr. f. d. ges. Neurol. u. Psychiat. **119**:277, 1929.

67. Dikshit, B. B.: Action of Acetylcholine on the "Sleep Centre," J. Physiol. **83**:42P, 1934.

68. Henderson, V. E., and Wilson, S. C.: Intraventricular Injection of Acetylcholine and Eserine in Man, Quart. J. Exper. Physiol. **26**:83, 1936.

69. Hess, W. R.: Ueber die Wechselbeziehungen zwischen psychischen und vegetativen Funktionen, Schweiz. Arch. f. Neurol. u. Psychiat. **15**:260, 1934.

70. Demole, V.: Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

Fischer [71] injected small amounts of Ringer solution, containing calcium chloride, into the region of the infundibulum of rabbits and cats and produced a state resembling normal sleep. Marinesco, Sager and Kreindler [66]; Lafora and Sanz,[62] and others produced sleep by intraventicular injections of calcium and elicited excitement, sometimes followed by delayed sleep, with potassium salts. Brunelli [72] found that certain ionic metals produce sleep, in the following order of efficacy: calcium, barium, strontium, magnesium, lithium, sodium and potassium. Cloëtta and Fischer [71] reported that there was an increase in the calcium concentration of the hypothalamus during narcosis. This observation, and the fact that the blood calcium falls during narcosis and sleep, led them to conclude that sleep is brought about by a shift of calcium from the blood to body tissues, including the hypothalamus. Katzenelbogen,[73] however, found no such increase of calcium in the brain during sleep, and Cooperman [74] disclosed that the fall in blood calcium during sleep occurs after the beginning of sleep and is coincident with bodily relaxation. According to Harrison,[50] there is no possible way to interpret the results of injections of calcium as phenomena of stimulation or excitation. Pharmacologically, it can be stated that there is insufficient evidence that the hypothalamus acts as a sleep center.

PSYCHOLOGIC CONSIDERATIONS

Normal sleep is essentially a biologic function, governed chiefly by the hypothalamus. The fact that man is able to fall alseep consciously or unconsciously on attempting to escape certain emotional difficulties or to keep awake voluntarily in emergency situations or under deep emotional strain would indicate that the higher cortical centers also play an important role in the regulation of sleep and in their influence on the hypothalamus. Examples of higher cortical influences on the regulation of sleep are numerous and were discussed in detail in another presentation (Davison [75]). It is also well to bear

71. Cloëtta, M., and Fischer, H.: Ueber die Wirkung der Kationen Ca, Mg, Sr, Ba, K und Na bei intrazerebraler Injektion (Beitrag zur Genese von Schlaf und Erregung), Arch. f. exper. Path. u. Pharmakol. **158**:254, 1930.

72. Brunelli, B.: Contributo alla fisiopatologia dei centre vegetativi del diencefalo con speciale riguardo al centro per la regolazione de sonuo e della veglia, Riv. biol. **14**:375, 1932.

73. Katzenelbogen, S.: The Distribution of Calcium Between Blood and Cerebrospinal Fluid in Sleep Induced by Diallyl-Barbituric Acid, Arch. Neurol. & Psychiat. **37**:154, 1932.

74. Cooperman, N. R.: Calcium and Protein Changes in Serum During Sleep and Rest Without Sleep, Am. J. Physiol. **116**:531, 1936.

75. Davison, C.: Psychological and Psychodynamic Aspects of Disturbances in Sleep Mechanism, Psychoanalyt. Quart. **14**:478 (Oct.) 1945.

in mind that cortical activity does not cease during sleep. Discoveries have been synthesized in sleep and dreams.

The hypothalamus, the main and most important vegetative center, plays a part not only in the control of water and carbohydrate metabolism, the maintenance of normal sleep rhythms and the stabilization of body temperature and cardiac, respiratory and gastrointestinal functions, but in the mechanism producing such emotions as fear, anxiety and anger. The hypothalamus is undoubtedly part of the motor mechanism through which emotional states are expressed. The influence of acute emotions on bodily functions is generally accepted today. It is needless to repeat the general bodily, and especially visceral, responses, including sleep, which may result from emotional disturbances, such as fear, anxiety, rages or unconscious repressed drives.

Until recently, it was thought that the state of sleep constituted merely a diminution or lessening in the general biologic activities of the organism. The act of sleeping, however, must also be considered as a fundamental psychobiologic protective function against physical and mental exhaustion, operating as a means of helping the person to keep up his instinctual equilibrium. Sleep, in other words, is a nightly regression, associated with a temporary denial of reality and apparent blocking of certain motor activities. Sleep or somnolent states and insomnia may thus assume the character of a psychophysiologic defense mechanism against dangerous collisions between the individual's drives and the surrounding world hostile to his instinctual demands. Sleep is a temporary, narcissistic withdrawal of the ego, or, as Freud [76] put it, a reenacting of the life in utero by refusing consciously to perceive stimuli from the external world. If one accepts the theories of unconsciousness, repression and regression and the freudian interpretation of dreams, it follows that sleep disturbances (insomnia and somnolence) occurring in the psychoneuroses, in twilight states and somnambulism (Davison [75]) and even in some organic diseases with psychoneurotic manifestations are retreats in order to avoid the unpleasant features of reality, the powerful and perverted instinctual drives. In other words, in sleep the person wishes to lose contact with the outer world and with reality. In some cases of somnolence the retreat is resorted to in order to obtain gratification—a wish fulfilment of the distorted instinctual drives.

As already indicated, every emotional situation is invariably associated with some physiologic response, such as sweating, palpitation, shortness of breath, pallor, blushing, changes in blood pressure, erection of hair, sphincteric disturbances, laughter, weeping and sleeplessness or somnolence. These physiologic responses take place when the

76. Freud, S.: Collected Papers, London, Hogart Press, 1933.

emotional causes of the psychologic conflict cannot be expressed and released through normal voluntary channels; i. e., they are repressed. These physiologic responses are undoubtedly mediated and controlled by the cortex, by the hypothalamus, and possibly by other subcortical structures. The repressed drives, such as sexual conflicts, hostility or guilt feelings, lead to chronic emotional tensions, which, in turn, result in dysfunction of the vegetative nervous system, with subsequent disturbances in digestion, respiration, circulation and sleep. It is impossible to understand or to study these emotional conflicts and their early influence on bodily changes, including sleep, with the present laboratory technical methods. They have to be approached through psychologic studies.

SUMMARY AND CONCLUSIONS

From the analysis of the clinicopathologic material presented, the cases reported in the literature and animal experiments, it is possible to reconstruct the centers and pathways concerned with the sleep mechanism.

The cases of cortical lesions indicate that fibers for the control of sleep may originate in the cerebral cortex, especially the hippocampal, cingular, frontal, premotor and temporal convolutions. To a certain extent, therefore, the hypothalamus is under cortical control. These impulses are mediated by voluntary and involuntary pathways. The main afferent and efferent pathways connecting the hypothalamus and the cortex are: (1) the medial forebrain bundle, which runs between the ventromedial olfactory correlation areas of the cortex and the preoptic and hypothalamic areas, and (2) the corticohypothalamic pathways, which are essentially the fornix and the inferior thalamic peduncle. The connection furnished by the latter fibers between the cortex and the hypothalamus is best illustrated by the cases of corticodiencephalic lesions. Other, less well established, corticohypothalamic pathways are the frontotuberal tract and the neocorticoseptal tract. There are experimental suggestions that in normal sleep the cortex becomes deafferented. Sleep, therefore, is impossible without the cortex. Forced wakefulness and diurnal sleep are cortical functions.

The evidence in the clinicopathologic cases of the diencephalic group and the results of other anatomophysiologic investigations indicate that the hypothalamus is the main center regulating sleep. The hypothalamus is in intimate connection with the thalamus, the striopallidum and the hypophysis, and its main afferent and efferent pathways are as follows:

1. Thalamohypothalamic and hypothalamothalamic pathways. They consist essentially of fibers from the medial and midline thalamic nuclei to the hypothalamic nuclei.

2. Thalamomamillary fibers. These pathways set up relays of somatic, visceral and sensory impulses from the neopallidum to the hypothalamus. The impulses from the hypothalamus to the thalamus are mediated via the mamillothalamic tract.

3. Mamillotegmental tract. This tract consists of fibers from the mamillary bodies terminating in the tegmentum.

4. Stria terminalis. This structure, which also contains preoptic and hypothalamic components, conveys fibers from the amygdaloid nucleus to the hypothalamus.

5. Supraoptic commissure.

6. Striopallidohypothalamic and subthalamohypothalamic pathways. The existence of such connections, reported by many observers, has not been fully accepted.

7. Hypothalamohypophysial pathways. These fibers run from the supraoptic, paraventricular and tuber nuclei to the neurohypophysis.

8. Interhypothalamic pathways. These fibers connect the various hypothalamic nuclei.

Lesions interrupting these pathways may lead to sleep disturbances. Some of our clinical material and the results of animal experimentation indicate that bilateral damage to the posterior part of the lateral hypothalamic area produces somnolence. When the waking center, the hypothalamus, is disturbed, somnolence ensues. The secondary involvement of the thalamic nuclei, striatum and pallidum in many of the clinicopathologic cases and the edema of these structures in the experimental animal suggest that these areas may also be concerned with regulation of sleep. Their influence, however, is mostly the result of involvement of the pathways which are in intimate association with the hypothalamus.

There is some evidence, largely clinical, that somnolence or other disturbances in the sleep mechanism may result from lesions at the mesencephalometencephalic level. These lesions were usually in the region of the periaqueductal gray matter. The known hypothalamic and mesencephalometencephalic connections are via (1) the mamillary peduncle, probably an ascending system of mesencephalic origin ending mostly in the lateral mamillary nucleus, and (2) mamillotegmental tract, an efferent pathway arising most likely from the dorsal part of the medial mamillary nucleus and terminating in the dorsal tegmental nucleus of the midbrain.

The opinion that somnolence and lethargy are related to lesions in the nuclei of the ocular nerves cannot be accepted, for these phenomena were essentially observed in the cases of the mesencephalometencephalic group and in some of the cases of the diencephalic group. The absence of such dysfunction in the other groups and the lack of sleep distur-

bances in other cases with ocular manifestations would seem to indicate that the various components of the ocular mechanism are not an indispensable part of the sleep mechanism.

Psychologic consideration of psychogenic disturbances and of some organic disorders with psychoneurotic symptoms indicates that the pathways and centers aforementioned, especially the hypothalamus, are important in the regulation of sleep. In most of the cases of psychogenic disorders sleep is a retreat in order to avoid the unpleasant features of reality, the powerful and perverted instinctual drives. In some cases of somnolence the retreat is resorted to in order to obtain gratification—a wish fulfilment of the distorted instinctual drives. The repressed drives lead to emotional tensions, which, in turn, result in dysfunction of the vegetative nervous system, of which sleep forms a part.

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EXTENSIVE EROSION OF THE BASE OF THE SKULL FROM A LEPTOMENINGEAL CYST

Report of a Case

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AND
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EROSION of the cranial bones from pressure of a leptomeningeal cyst is an uncommon, but not rare, condition. While the majority of such cysts develop after severe trauma to the skull, usually with fracture, there is evidence that congenital abnormalities in the dura and leptomeninges may contribute to their production. Haymaker and Foster [1] reported a case in which a large collection of clear, colorless fluid resembling cerebrospinal fluid was found enclosed between the two layers of the dura in the posterior cranial fossa; a small defect was present beneath the tentorium, through which a lobule of the cerebellum was herniated. While their patient gave a history of a fracture of the skull in childhood, the separation of the dural layers and the small subtentorial defect may have been congenital abnormalities which favored development of a cyst in this location.

Leptomeningeal cysts have been noted more commonly in the parietal, frontal and occipital regions. In the case to be described a difficult diagnostic and therapeutic problem was presented by the presence of an extensive area of destruction of bone in the floor of the middle cranial fossa.

REPORT OF CASE

A 28 year old soldier was admitted to an Army general hospital with swelling about the right orbit and temporozygomatic region and with exophthalmos on the same side. One and one-half years before, in North Africa, the patient had received a mild cerebral concussion as a result of an explosion of several large bombs. The following morning he noticed swelling of the right temple and slight exophthalmos. These symptoms persisted for several days and then disappeared, but he continued to have occasional dull, aching pains in the right orbital region, which were relieved by analgesics. One year later he had pneumonia and was hospitalized. It was then noted that there were slight swelling of the temple and slight exophthalmos on the right side, with slight constriction of the right pupil. No other abnormal physical or neurologic signs were present. Roentgenographic examination of the skull revealed a group of cystic-appearing shadows in the right anterior temporal region and in the superior, posterior and lateral

1. Haymaker, W., and Foster, M. E., Jr.: Intracranial Dural Cyst, with Report of a Case, J. Neurosurg. **1**:211-217, 1944.

walls of the right orbit with thinning of bone in these regions. It was thought that the patient had an expanding cystic tumor of bone, or possibly a vascular neoplasm. Because of the apparent rapidity of growth, he was evacuated by air to the United States.

Examination.—On admission to an Army general hospital, the patient was entirely asymptomatic. Examination showed pronounced exophthalmos of the right eye and bulging of the entire right temporozygomatic region without discoloration. The swelling was moderately firm, nontender and slightly pulsatile. The margins were ill defined, but the swelling appeared to be limited below by the zygomatic arch and lateral wall of the maxilla. There were no palpable nodes in the neck or the preauricular region. Extraocular movements were normal, and there was

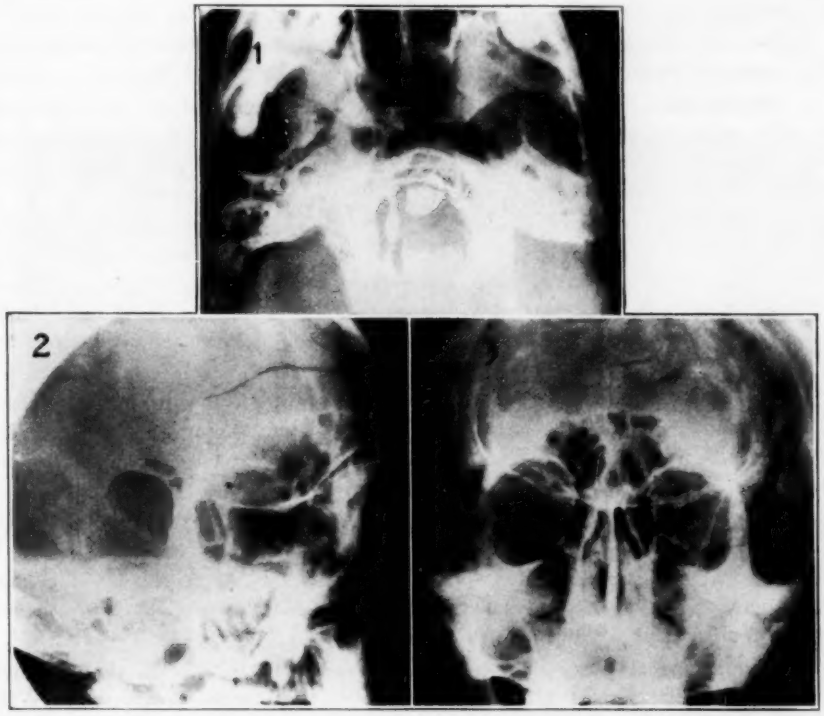

Fig. 1.—*1,* verticosubmental projection, demonstrating erosion of the sphenoid bone on the right. An expansile mass crosses the midline. *2,* oblique projection of the orbit, revealing erosion of the sphenoid bone behind the lateral rim of the orbit. *3,* posteroanterior projection, demonstrating erosion of the greater and lesser wings of the sphenoid bone on the right.

no increasse in intraocular tension. Vision was 20/20 in each eye, and the visual fields and fundi were normal. The remainder of the physical examination was noncontributory.

Roentgenographic examination of the skull revealed an extensive destructive lesion involving almost all the greater wing of the sphenoid bone on the right, the more lateral portion of the lesser wing and the body of the sphenoid bone behind the sphenoid sinus, where it crossed the midline (fig. 1*1*). There was visible erosion of the walls of the foramen lacerum medium, the foramen ovale and the foramen spinosum on the right. There was also extension across the

sphenotemporal suture into the more anterior part of the squamous portion of the temporal bone. While the process was almost wholly osteolytic, at the margins in several places a fine line of density demarcated the lesion from the adjacent normal bone. There was no evidence of increased vascular markings in the skull near the lesion, and no other abnormalities were noted. The sella turcica and the paranasal sinuses were of normal appearance. Conventional posteroanterior and lateral roentgenograms were less informative than stereoscopic projections of the base (verticosubmental, fig. 1 *1*) and of the orbits (optic canal position, fig. 1 *2*).

Pneumoencephalographic studies showed normal distribution of gas in the ventricles and the basal cisterns. No gas was noted in the subarachnoid space about either temporal lobe. There was no evidence of dilatation, asymmetry or displacement of the ventricles.

Laboratory studies revealed nothing abnormal.

Differential Diagnosis.—A number of conditions were considered in the diagnosis, some of which were ruled out, for obvious reasons.

1. Meningioma: While there was extensive involvement of the sphenoid bone, the ridge appeared to be intact, and there was no evidence of hyperostosis of the ridge or of the olfactory groove. The absence of abnormality revealed by the cerebral air study offered additional evidence against this diagnosis.

2. Epidermoid Tumors or Cholesteatoma: The majority of such tumors which have acquired the large size of the lesion noted in this case present dense, irregular borders, and the bone within shows patchy erosion with islands of noneroded bone remaining, thus giving a mottled, or honeycomb, appearance. However, in rare cases there may be complete loss of bony structure. It was felt, therefore, that the diagnosis of such a tumor could not be excluded.

3. Osteogenic Sarcoma: A tumor of the osteolytic type is rare in this location; the extension of the process across the sphenotemporal suture and the fine line of density demarcating the margins of the lesion were evidence against this diagnosis.

4. Xanthomatoses (including eosinophilic granuloma): While single cranial lesions are less common than multiple, the roentgenographic appearance may be similar to that noted in this case. The characteristic finding is that of a punched-out lesion with sharply outlined margins. It was felt that the diagnosis of such a lesion could not be excluded.

5. Leptomeningeal Cyst: The history of previous trauma to the skull followed by destructive change in the bone is suggestive; the location is unusual. While thinning, bulging and central erosion of bone are noted commonly over a cyst, there is rarely complete loss of bone over a wide area. It was believed that the diagnosis of such a lesion was possible but not probable.

6. Myeloma: Solitary myelomas are found occasionally in the skull, but rarely do they acquire the size noted in this case without secondary or accompanying lesions elsewhere. Moreover, they are more likely to occur in older people.

7. Metastatic Malignant Disease: The absence of multiple lesions offered evidence against the diagnosis of this condition.

8. Localized Osteitis Fibrosa Cystica: In reported cases there is expansion of the diploe with thinning, but not destruction, of the inner and outer tables. It was believed that the diagnosis of such a condition could be excluded.

Operative Observations.—With endotracheal anesthesia, a hidden frontotemporal incision was made. When the temporalis muscle was incised and reflected, a membrane was found to bulge through a large area of erosion in the greater

wing of the sphenoid bone and the anterior margin of the squamous portion of the temporal bone. A needle was inserted through the membrane, and about 10 cc. of clear, watery fluid was aspirated. This white, thick-walled cyst appeared to be extracranial, but by continued exploration it was found that this was only a small locule of a larger, thin-walled cyst, which was apparently covered by dura. The lateral wall of the right orbit was found to be paper thin, mobile and displaced inward by an extension of this cystic mass. It was then found that this larger cystic mass extended downward along the base of the middle cranial fossa, with complete loss of bony structure downward and forward as far as the pterygoid fossa anteriorly, the body of the sphenoid bone medially and the styloid process of the temporal bone posteriorly. The gasserian ganglion and the maxillary and mandibular nerves were exposed, and the cystic mass was dissected from them. The temporal lobe of the brain was exposed at its tip, where there were some adhesions to the meninges about the neck of the large sac. Small hemostatic clips were inserted to show the limits of the dissection (fig. 2). The large cavity occupied by the cyst was filled with fibrin foam in thrombin, and fascia from the

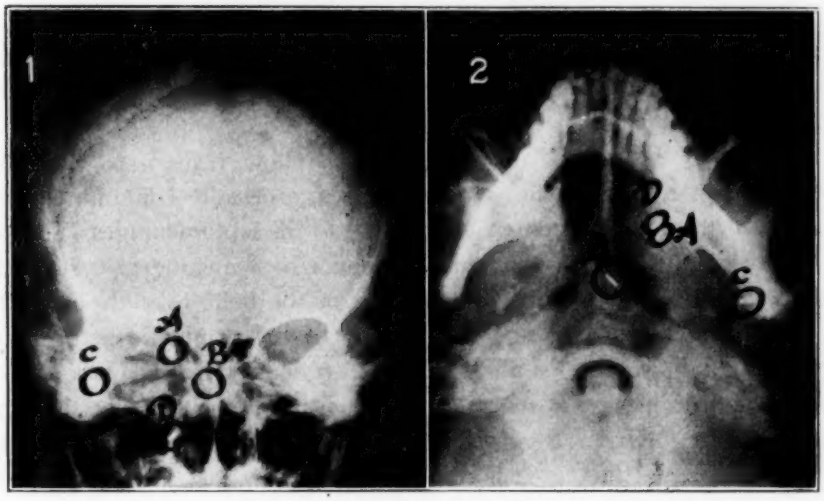

Fig. 2.—*1*, posteroanterior projection (postoperative), showing hemostatic clips at the margins of the area of operative exploration. *A* is placed at the junction of the body and the right greater wing of the sphenoid bone; *B*, within the body of the sphenoid bone, behind and below the sphenoid sinus; *C*, in the most posterolateral portion of the lesion, lateral to the temporal lobe, and *D*, in the most inferior portion of the lesion, behind the right pterygoid process. *2*, vertigosubmental projection (postoperative).

temporalis muscle was used to repair the dural defect. The wound was closed, using interrupted sutures in the temporalis muscle and the skin.

Examination of fluid removed from one of the cysts revealed 1 leukocyte per cubic millimeter, 15 mg. of sugar and 217 mg. of total protein per hundred cubic centimeters, a strongly positive reaction for globulin and 600 erythrocytes per cubic millimeter.

Microscopic sections of the membrane of the cyst showed a thin fibrocollagenous wall lined with flattened cells. There was a well vascularized fibroblastic zone incorporating hyaloid and collagenous foci, which probably represented villous processes arising from the wall. The histopathologic picture suggested that the

tissue was dura mater and neomembrane which had undergone collagenous degeneration.

Postoperative Course.—The patient made an uneventful recovery except for paralysis of the right lateral rectus muscle and resultant diplopia, both of which disappeared within two months.

COMMENT

Collections of fluid, clear or xanthochromic, within the subarachnoid or subdural space or between layers of the dura have been noted after trauma, and occasionally as sequelae of meningoencephalitis. The mechanics of production is not thoroughly understood; however, it is probable that as a result of injury or infection arachnoid granulations develop, with production of adhesions. If these adhesions are so disposed as to close off a portion of the subarachnoid space, it is believed that one or more cysts may form. Leptomeningeal cysts have been reported as occurring in practically all portions of the subarachnoid space, including the basal cisterns, the space over the cerebral and cerebellar hemispheres and even within the cortical sulci. At times, because of size and location they may produce clinical effects similar to those noted with neoplasms.

According to Dyke,[2] the cysts which follow trauma to the skull are more apt to result from severe injuries, especially comminuted and depressed fractures with extensive damage to the leptomeninges. Months or years later there may be clinical evidence of a meningeal cyst at the site of injury, with thinning and bulging of the bone over the cyst and frequently persistence or actual widening of the original fracture line. The inner table of the skull is usually eroded, with production of a scalloped effect near the margins of the cyst. Rarely, as in the case reported here, there are complete erosion of both tables and bulging of the cyst into the pericranial soft tissues. About the margins of the lesion there may be evidence of hypervascularity of the bone.

Schwartz [3] called attention to a lesion which is noted in occasional cases—the presence of irregular areas of thickening of the bone of the inner table over a cyst. He expressed the belief that these areas are due either to the healing of an antecedent fracture or to an atypical reaction of the bone to the underlying cyst.

Some leptomeningeal cysts produce no recognizable change in the cranial bones. If such a lesion is suspected, pneumoencephalographic studies may be of assistance in identification and localization.

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2. Dyke, C. G.: The Roentgen-Ray Diagnosis of Diseases of the Skull and Intracranial Contents, in Golden, R.: Diagnostic Roentgenology, New York. Thos. Nelson & Sons, 1941, chap. 1, pp. 302-331.

3. Schwartz, C. W.: Leptomeningeal Cysts from a Roentgenological Standpoint, Am. J. Roentgenol. **46**:160-165, 1941.

It is of interest in this case that the entire cyst appeared to lie completely outside the cranial cavity, owing to the extensive area of erosion of bone. It may be that much of the pressure erosion came from without, after the cyst had once herniated through the floor of the middle cranial fossa. This fact is probably responsible for the absence of symptoms and neurologic signs.

SUMMARY

A case of leptomeningeal cyst of the right middle cranial fossa, following injury one and one-half years before operation, is reported.

The unusual feature of the case was the extensive destruction of bone in the middle cranial fossa, with complete erosion of both tables of the skull and herniation of the cyst into the pericranial tissues.

PAROXYSMAL AUTONOMIC CRISES IN THE POSTENCEPHALITIC STATE

Report of a Case

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PHILADELPHIA

PAROXYSMAL autonomic crises or attacks as a manifestation in the postencephalitic state have not been described in standard neurologic textbooks. Reports of this syndrome in the literature have been exceedingly rare in spite of the voluminous material on the sequelae of epidemic encephalitis. Consequently, when one is confronted with the striking group of symptoms that constitute the autonomic crisis in postencephalitic patients, many apparently new and troublesome questions present themselves. For this reason the following unusual case is reported.

REPORT OF CASE

The patient, a 41 year old Negro, had a high school education and was rather intelligent. The family history was noncontributory. In 1918, at the age of 15, he had a severe bout of "influenza," and in the following year he exhibited behavior difficulties, necessitating his remaining away from school for about a year. In 1923, at the age of 20, he had an attack or a relapse of encephalitis, during which he remained unconscious for thirty-six hours. In subsequent years there was progressive development of the defects of paralysis agitans with locomotor and speech troubles. In addition, he exhibited various antisocial trends and behavior complications. He served several terms in jail for a number of misdemeanors and finally received, in 1939, a six to nine year sentence for attempted rape of a woman who kept house for him.

During the three years prior to his admission to the state hospital, while he was still in prison, the patient became subject to peculiar attacks, which became progressively more frequent and more intense. These attacks were described by the prison medical authorities as temper tantrums or outbursts of violence and by the patient himself as "spells of cramps in the legs and hollering." These attacks finally became so severe that the patient was transferred to the Philadelphia General Hospital, in September 1944, for possible commitment to an institution for the insane.

On the fifth day after his admission to the Philadelphia General Hospital he suddenly became agitated, excited and noisy. It was noted by the resident that he had tonic contractions of the muscles and that he sweated profusely. His pulse was recorded as 140 per minute and his temperature as 101 F. In two hours the pulse rate and temperature were back to normal, and the patient returned to

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From the Philadelphia State Hospital and the Department of Neurology, University of Pennsylvania Graduate School of Medicine.

This case was reported at a meeting of the Philadelphia Neurological Society, April 27, 1945.

his previous state of composure. The physician in charge expressed the opinion that this peculiar episode was an anaphylactic reaction to 10 drops of tincture of stramonium given a few minutes previously and set about proving his point by administering minute doses of the drug. However, there was no further recurrence, and the patient was transferred to the Philadelphia State Hospital on Oct. 16, 1944.

On admission he presented a picture of advanced paralysis agitans, with the typical facies, posture, gait, slowness of muscular response and rigidity. There were, however, essentially no tremors except those of the tongue and mouth when he attempted to speak. Speech was impaired by interminable trembling, stuttering and repetitiousness to the extent that it was difficult to understand him. The pupils were unequal, the right being about 3 mm. and the left 2 mm. in diameter. They did not react to light or in accommodation. Convergence was poor, and there was vertical nystagmus on both upward and downward gaze. Otherwise, the neurologic examination showed an essentially normal condition. He weighed 131

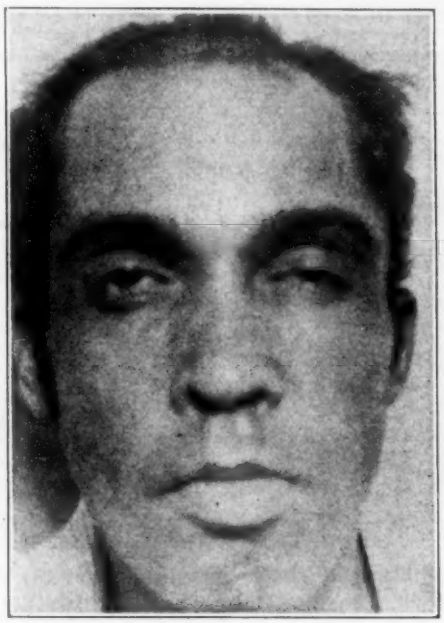

Fig. 1.—Patient as he appeared on admission to the Philadelphia State Hospital.

pounds (59.4 Kg.) and showed considerable emaciation. There was drooling of saliva from the mouth, and the face was greasy with excessive sebaceous secretion. The blood pressure was 100 systolic and 60 diastolic; the pulse rate was 80, and the temperature and respiration were normal. No other abnormal signs were noted. He was mentally clear and alert, but conversation could be carried on only with great difficulty because of his speech troubles.

The urine was normal. The blood urea measured 11 mg. and the blood sugar 70 mg. per hundred cubic centimeters, and the Wassermann reaction of the blood was negative. The spinal fluid was clear and under normal pressure and contained no cells; the Wassermann reaction was negative, and the colloidal gold curve was normal. Roentgenograms of the skull and the chest were normal.

About two weeks after his admission he had the first of the many episodes which came under my observation. These attacks occurred on the average of

perhaps once a week. They differed somewhat in intensity, so that they could be described as light or severe. The majority were severe. A description of a typical attack follows:

The patient becomes restless and begins to groan. The groaning grows louder, shriller and more frequent, occurring more or less synchronously with expiration, until it resembles the barking of a dog. When questioned at this stage he points to his legs and cries, "Cramps in the legs; cramps in the legs; cramps in the legs"! Within one-half hour to an hour the legs are extremely rigid and hyperextended, so that at times the body is lifted from the bed, resting on the heels and shoulders. There are rapid trembling of the entire body, especially the legs, and a peculiar flapping of the forearms and hands; and in general he shows extreme agitation, so that it is necessary to use physical restraint. Respiration by this time is panting and reaches a rapidity of 60 or more per minute. The body is drenched in profuse perspiration, and the sheets of the bed not only are soaked but gather pools of moisture. The pulse rate is 160 per minute, and the temperature (rectal) at its height is 106.5 F. The blood pressure is 80 systolic

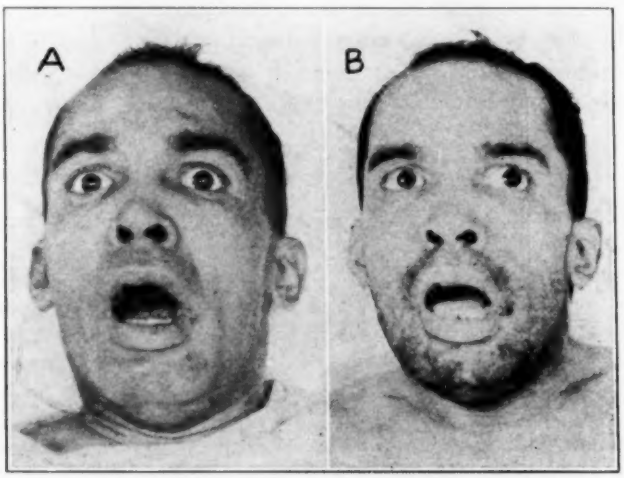

Fig. 2.—*A*, patient during an autonomic attack. Note the bulging eyes, panting nostrils and dripping streaks of perspiration. *B*, patient in another autonomic paroxysm.

and 40 diastolic. The face looks wild, presenting an expression between panic and rage. The eyeballs protrude, and the pupils are widely dilated. He strikes at every one approaching him. All these symptoms reach their peak in three or four hours and abate in six to eight hours. Subsequently the patient is exhausted, quiet and sleepy. Later still he is back to his usual status. He apologizes to any one whom he may have struck during his peculiar outburst. He cannot explain why he should strike any one. He has an excellent recollection of all that has taken place. He describes his spell as an attack of cramps in the legs. (Figs. 2 and 3.)

The foregoing description is that of a severe, but fairly typical, episode. There were variations, however, particularly as regards intensity and duration. Mild attacks had a duration of only one or two hours, and one very severe episode lasted about twenty-four hours. There were mild episodes in which the chief symptoms were muscular rigidity and cramps, with no significant changes in respiration, pulse or temperature. The highest recorded temperature was 106.7 F.

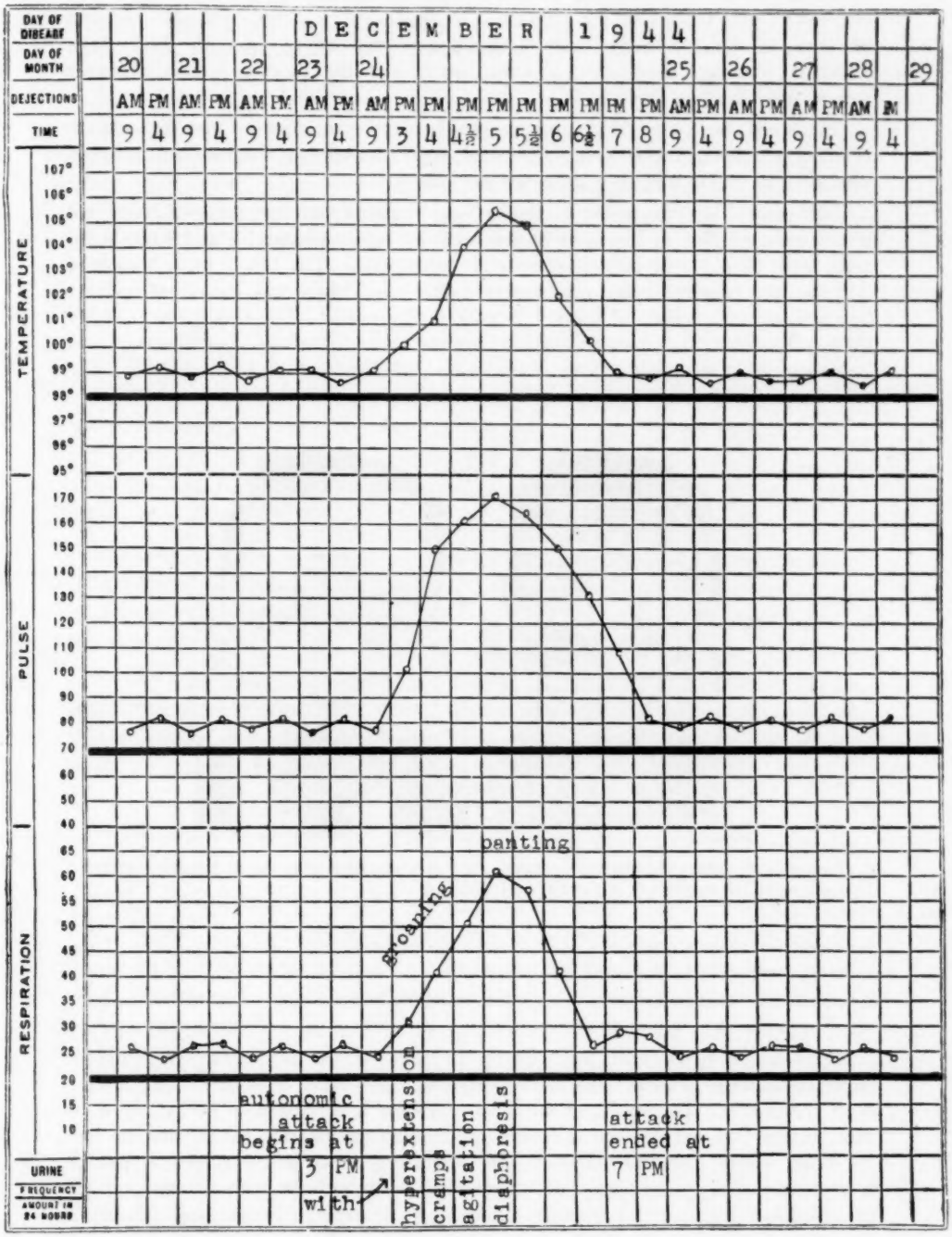

Fig. 3.—Chart showing the respiration, pulse and temperature curves during a paroxysm.

Usually, however, the elevation was to 104, 103 or even 101 F. In one attack, while the temperature did not exceed 101 F., the pulse rate rose to 180 and the respiratory rate to over 60 per minute. The frequency of attacks was also variable, so that at their oftenest these episodes occurred every two or three days. Usually, however, they were a week apart, and the longest interval between attacks was fourteen days.

It should be added that interspersed between the attacks, and bearing no relation to them, there were occasional mild oculogyric spasms, which were, however, so slight that they attracted no attention.

Laboratory studies made during a severe paroxysm revealed 4,370,000 red blood cells, 13 Gm. of hemoglobin per hundred cubic centimeters and 9,600 white cells, with 67 per cent polymorphonuclear leukocytes. The blood sugar measured 202 mg. per hundred cubic centimeters. The spinal fluid was clear and under a low pressure of 50 mm. of water. It contained no cells. The total protein of the fluid measured 29 mg., the sugar 38 mg. and the chlorides 650 mg., per hundred cubic centimeters. A roentgenogram of the chest again showed nothing abnormal, and

Fig. 4.—*A*, patient about two months after he was placed on scopolamine therapy; *B*, patient as he appeared at the time of writing.

neither clinical nor roentgenographic examination revealed any enlargement of the liver or spleen. A painstaking examination of several specimens of the blood, taken at the height of fever, revealed no malarial organisms. Agglutination tests were negative for typhoid, relapsing fever and infection with Brucella abortus.

It is to be noted that this patient, in spite of the advanced symptoms of paralysis agitans present for many years, had not received any of the routine drug treatments. He was kept without drugs for a considerable period while at this hospital for purposes of observation. It was during this period that he had his most severe episodes. During the attacks he was given various types of treatment, including subcutaneous injections of caffeine and sodium benzoate and of morphine sulfate and intravenous injections of atropine sulfate and of sodium amytal. None of these drugs had any beneficial effect. The sodium amytal definitely aggravated the attack. Its injection resulted in considerable coughing and bronchial secretion and delay in the return of the temperature and pulse to normal. It was finally noted that injection of 1/75 grain (0.8 mg.) of

scopolamine hydrobromide terminated the episode within one-half to one hour. This drug was subsequently resorted to for control of the attacks. The patient was ultimately placed on regulation treatment consisting of oral administration of scopolamine hydrobromide, 1/75 grains three times a day.

He was observed for a period of two months while receiving treatment and for a similar period while without treatment. During the period of the treatment he had five attacks, all of which were relatively mild and of short duration. During the two months in which he was without treatment he had ten attacks, most of which were severe. Moreover, between attacks he was rather feeble, could scarcely walk and spent a great deal of time in bed, whereas with treatment he was ambulatory, cheerful and helpful about the ward (fig. 4 *A*).

COMMENT

The phenomenon of crises of the autonomic system in the postencephalitic state is so little known that when it does occur it presents considerable difficulty in diagnosis and interpretation. Thus, the episodes exhibited in the case reported here were considered by the medical authorities of the prison hospital as psychically induced temper tantrums, while a resident at a general hospital suspected that he was dealing with a drug sensitivity. Another physician, impressed by the paroxysms of high temperature, considered a diagnosis of malaria likely. The course of events and a more thorough investigation made the true character of the symptoms apparent. The phenomena displayed during the attacks can be subdivided physiologically into a group involving the vital autonomic functions, including tachycardia, tachypnea, diaphoresis and hyperthermia; a group expressing emotional release, resembling "sham" rage, and a group concerned with manifestations of muscular release, including pronounced rigidity, hyperextension, tremors and agitation.

The role of the diencephalon, in particular the hypothalamic region, as the center of the autonomic and emotional functions has been adequately established by the experimental work of Bard,[1] Ranson, Cannon,[2] Cushing[3] and others. Paroxysmal autonomic release phenomena as a clinical manifestation was first reported by Penfield[4] in a patient who was found to have a tumor involving the diencephalon. Paroxysmal autonomic episodes in the postencephalitic state have previously been

1. Bard, P.: The Hypothalamus and Sexual Behavior, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:551, 1940.

2. Cannon, W. B.: The Wisdom of the Body, ed. 2, New York, W. W. Norton & Company, Inc., 1939; Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton-Century Company, 1915.

3. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C Thomas, Publisher, 1932.

4. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

reported in only 3 or 4 instances. Wimmer,[5] of the Copenhagen clinic, in his monograph on the sequelae of epidemic encephalitis, described a case in which paroxysmal episodes of agitation and muscular spasms were associated with excessive perspiration, tachypnea and rapid, regular pulse, but with no rise in temperature. Neal,[6] in her volume on encephalitis lethargica, sponsored by the Mathison Commission, in which she summarized the work on hundreds of cases of encephalitis, did not mention this syndrome at all but did refer to the well known fact that there are autonomic disturbances in the postencephalitic state. Borremans and van Bogaert [7] reported 2 clearcut cases of paroxysmal vegetative syndromes associated with postencephalitis which, in the essentials, resembled the case here reported, as well as Penfield's case. In 1 of their cases autopsy revealed characteristic changes in the substantia nigra, as well as peculiar, Alzheimer-like changes throughout the diencephalon, from the region of the thalamus to the oculomotor nucleus. In 1943 Ostow [8] reported a case of a patient with postencephalitis who had attacks in which, in addition to cataleptic manifestations, such as akinesia, rigidity and mutism, he exhibited autonomic reactions, consisting of diaphoresis, rapid pulse (110 to 140 a minute), fever (100.6 F.) and hypertension. It must therefore be concluded that diencephalic paroxysms in their extreme form constitute a relatively rare occurrence in the postencephalitic state. Indeed, during a period of over five years of almost daily observation of, and close contact with, about 100 patients with paralysis agitans in various stages of advancement, I have not come across another case of similar attacks, although oculogyric crises were commonplace. It might be that in a mild form these episodes go unnoticed. It should also be noted that this patient, although having had postencephalitis for about twenty years, had had no previous routine drug therapy, and this may have had something to do with the occurrence of the attacks. As a matter of fact, the episodes were greatly reduced in intensity and frequency on the institution of regular treatment with scopolamine. The pathophysiology of the syndrome cannot be discussed here except to point out that this syndrome is another example of the numerous episodic manifestations that are common in this disease, as witnessed by oculogyric spasms, cataplexy,

5. Wimmer, A.: Further Studies upon Chronic Epidemic Encephalitis, London, William Heinemann, Ltd., 1929.

6. Neal, J. B., and others: Encephalitis: A Clinical Study, New York, Grune & Stratton, Inc., 1942.

7. Borremans, P., and van Bogaert, L.: Paroxysmal Vegetative Syndromes of Central Origin: Two Cases, Presse méd. **44**:1091 (July 4) 1936.

8. Ostow, M.: Recurrent Autonomic Phenomena Associated with Exacerbations of Postencephalitic Parkinsonism: Report of a Case, Arch. Neurol. & Psychiat. **50**:342 (Sept.) 1943.

narcolepsy, hyperkinetic attacks, tonic fits, temporary psychoses, hallucinations, compulsions and emotional outbursts.

SUMMARY

A case of paroxysmal autonomic crises occurring in a patient with postencephalitis is reported. The attacks consisted in the sudden appearance of extreme tachycardia, tachypnea, hyperthermia and diaphoresis, associated with emotional manifestations resembling "sham" rage and with pronounced muscular hypertonic phenomena. Some of the difficulties and errors of diagnosis are discussed. A survey of the literature reveals that this syndrome is a rare sequel of the postencephalitic state. The attacks could be partially controlled by the subcutaneous administration of 1/75 grain (0.8 mg.) of scopolamine hydrobromide and were considerably reduced in intensity and severity by regular scopolamine therapy.

NOTE.—The preceding report covered the period of the patient's progress up to March 15, 1945. On April 27, 1945, the case was presented before the Philadelphia Neurological Society. The following report is a summary of what has happened to the patient since.

On March 15, 1945, treatment was changed to include amphetamine sulfate, 10 mg., twice a day, in addition to the usual administration of 1/75 grain of scopolamine hydrobromide three times a day. The patient has been on this regimen up to the time of writing, Sept. 15, 1945. During this period of six months he has had one major autonomic crisis, which occurred on April 26. He has had none since. There have been instead minor attacks of a sort which do not differ much from the spells commonly seen in other patients with encephalitis and which do not attract any particular attention. They last about one-half to one hour and consist primarily of an exacerbation of rigidity with or without oculogyric phenomena. They occur infrequently, on an average of about once a month.

The patient has otherwise done well. He has gained about 40 pounds (18 Kg.), now weighing 170 pounds (77.1 Kg.). He is comfortable, up and about and helpful with ward work. He still shows the usual neurologic picture of severe paralysis agitans, his speech particularly being greatly affected, but there are essentially no tremors.

It seems, therefore, that his present therapeutic regimen, consisting in the combined use of large doses of scopolamine and amphetamine, is effective in eliminating or reducing to insignificance his previous autonomic paroxysms, which were of such severity that each one of them threatened to terminate his life. The efficacy of this combination for the control of severe symptoms, especially of a paroxysmal nature, in patients with postencephalitis is thereby reaffirmed.

DISCUSSION

DR. BERNARD J. ALPERS: One feature of this case interested me particularly. I wonder whether this man actually showed rage during the course of the outbursts. Was it rage, or was it a reaction of pain to the cramps in his legs? It looks as though it might have been the latter. In other respects the case resembles very much that of diencephalic epilepsy described by Penfield.

I have seen what seem to be two types of diencephalitis in children. One was that of a girl addicted to phenobarbital who had a typical syndrome of this sort, with changes in sweating, pulse and temperature during the course of her attacks. These symptoms disappeared when she recovered, and several months later she had had no more of the episodes.

DR. CHARLES RUPP JR.: I wonder whether Dr. Oller attempted to precipitate any of these attacks by administering drugs intravenously or intramuscularly. I recall several years ago giving epinephrine intravenously to an extremely depressed patient in order to investigate the hysterical manic attacks, which were somewhat similar to those Dr. Oller described, and the patient went into a manic-like episode for a short period.

DR. FRANCIS M. FORSTER: I should like to ask whether Dr. Oller had an opportunity to get an electroencephalogram during one of these spells.

DR. CHARLES I. OLLER: The main reason for presenting this case was to bring to attention a striking, though rare, manifestation in the postencephalitic state, namely, autonomic fits.

With regard to Dr. Alper's question whether there was actually an element of rage or whether the patient's behavior was mere expression of pain, one has as evidence, in addition to the facial expression, which of course is not specific, the fact that the patient would strike at all those about him, without any reason, after which he was always sorry.

I was not interested in precipitating any attacks with the use of sympathetico-tonic drugs, since I was more anxious to terminate them when they occurred, inasmuch as the patient was often deathly sick with them.

No electroencephalographic study was made, as it did not seem to me that the results would contribute to an understanding of the case.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

INHIBITION OF ACTIVITY IN SINGLE AUDITORY NERVE FIBERS BY ACOUSTIC STIMULATION. ROBERT GALAMBOS and HALLOWELL DAVIS, J. Neurophysiol. **7**:287 (Sept.) 1944.

Galambos and Davis studied by means of microelectrodes the nerve impulses in a single auditory nerve fiber. The spontaneous discharges which occur in silence in some fibers can be stopped by certain tones or noises. Inhibitory and excitatory tones for each fiber fall into a definite range of frequencies, but there is no common relation between fibers as to the relationship of these inhibitory and excitatory frequency ranges. The discharge excited by an adequate tone also can be reduced or abolished by the simultaneous presentation of a second tone, when the inhibitory areas may encroach on and overlap the response area. The inhibitory action of low tones on activity aroused by high tones is more widespread than the inhibitory influence exerted by high tones over the excitatory action elicited by low tones. The mechanism of the inhibition is unknown. Factors referable to the middle and inner ear have been excluded. The authors suggest that nerve fibers underlying the organ of Corti play a role. The function of the inhibition is obscure, but it seems probable that it plays a role in the phenomenon of masking.

FORSTER, Philadelphia.

INFLUENCE OF CONDITIONING NERVE STIMULI ON RELAYED VOLLEYS EVOKED FROM SPINAL CORD: PERIODIC FACILITATION AND INHIBITION. CARL GUSTAF BERNHARD, J. Neurophysiol. **7**:397 (Nov.) 1944.

Bernhard stimulated locally by means of electrodes placed laterally in the spinal cord and elicited a number of oscillations of synchronized impulses in the peroneal nerve. The various synchronized waves of this complex response could be inhibited or facilitated by conditioning stimuli administered to the ipsilateral popliteal nerve, depending on the time interval between the conditioning and the test stimulus. The conditioning stimulus administered to the popliteal nerve produced a rapid periodic variation of inhibition and facilitation, with four inhibitory minimums and four excitatory maximums. The number of depressions and facilitations may vary from experiment to experiment, but the temporal location with reference to the conditioning stimulus is constant.

FORSTER, Philadelphia.

EYE MOVEMENTS IN ELECTRICAL SHOCK PROCEDURE. F. F. KINO, J. Ment. Sc. **90**:592 (April) 1944.

Kino found that patients subjected to electric shock therapy always showed lateral deviation of the eyes in the same direction. Usually there was faint homonymous deviation of the head, but some patients kept the head turned straight forward or turned it to the opposite side. The number of patients deviating the eyes to the left was about equal to the number deviating to the right. Right or left handedness has no bearing on the direction of deviation, nor does age, sex or character of the mental disturbance.

The direction of deviation of the eyes could be reversed in many patients by having them fix their gaze in the direction desired for two or three minutes before shock was given. A few failed to show deviation of the eyes to either side after this effort. Many showed deviation similar to that they had presented before,

i. e., without previous fixation of gaze. Other workers had shown that stimulation of one or the other frontal adverse visual fields would produce conjugate deviation to the opposite side. The observations presented by Kino showing bilateral response after bilateral simultaneous stimulation led him to conclude that since the deviation is always the same in a given case its direction cannot be due to external factors but must be inherent in the physiology of the subject; it must be based on a difference in degree or duration of a sustained excitation in both adversive visual fields. The effect of conscious inhibition on one visual field prior to shock is in keeping with this observation.

McCarter, Boston.

Experimental Edema of the Brain: II. Factors Which Influence the Edema. S. Obrador Alcalde and J. Pi-Suñer, Bol. d. Lab. de estud. med. y biol. **1**:80 (May) 1942.

Obrador Alcalde and Pi-Suñer report on various factors which affect the cerebral edema produced in dogs by lesions of the floor of the fourth ventricle. 1. Posture influences the intensity of the edema. When the animal lay on one side, the edema was more pronounced in the inferior hemisphere. Changing the position of the animal once the edema had appeared sometimes altered the size of the swollen hemisphere. 2. Asphyxia has no effect. The edema was the same whether or not artificial respiration was given. This was noted to be true in spite of the fact that changes in respiratory rhythm were frequent after the experimental lesions. 3. Sympathectomy has no effect on the intensity of the edema. Ligation of both carotid arteries before the lesions of the fourth ventricle were produced did not prevent appearance of edema. Cutting of the ligatures and reestablishment of the cerebral circulation did not increase the amount of cerebral herniation. In only 1 animal, with extreme edema, did a drop in blood pressure and ligature of the carotid arteries cause mild diminution of the edema. There was no change in the edema after lowering of the blood pressure in any of the other animals. 4. Drugs have varying effects. Intravenous injections of epinephrine caused an increase in the edema in some cases. This increase was transitory and paralleled the increase in blood pressure. Intravenous injection of small doses of ergotamine tartrate (0.25 mg.) did not affect the blood pressure or the cerebral edema. Repeated injections of small doses (up to a total of 1 mg.) had no effect on the neurogenic cerebral edema. The injection of larger doses (0.5 mg. or more) increased the blood pressure and caused a marked increase in existent edema. The injection of adrenal cortex extract (natural and synthetic), even in large doses, did not modify the edema. In 6 of 9 animals intravenous injection of hypertonic solutions caused striking diminution to disappearance of the edema. The edema was induced again by a new lesion in the region of the fourth ventricle and was readily diminished by a second injection of a hypertonic solution.

Savitsky, New York.

Experimental Epilepsy in Man. Isaac Roimiser, Rev. neurol. de Buenos Aires **7**:241 (July-Sept.) 1942.

Roimiser reviews the literature on experimental epilepsy and points out that up to the present time convulsive agents have been able to produce only the motor phase of epilepsy. He repeated the use of metrazol in 10 cases of various types of epilepsy, the drug being given in subconvulsive doses. In all cases the seizures characteristic of the particular patient were reproduced faithfully. They included petit mal, psychomotor equivalents, obnubilation, tonic spasms, clonic local or generalized convulsions and sensations similar to spontaneous auras.

The drug was injected in various quantities at different times in order to obtain the optimal dose for the desired effect, 2 to 2.5 cc. usually being sufficient. In 1 case, in which 3 cc. provoked a major spell, one-half that quantity led to an attack of petit mal. The patient had suffered from both major and minor seizures.

The author concludes that metrazol permits the experimental study of epilepsy in man in an objective and controllable manner. In epileptic persons with adequate technic it is possible to reproduce faithfully all types of spontaneous spells, not only the typical motor crises but partial seizures, formes frustes and equivalents.

PIETRI, New York.

Neuropathology

SPINAL VEGETATIVE CENTERS: II. SPINAL TROPHIC CENTERS. O. GAGEL and L. CZEMBIREK, Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:644 (April) 1941.

Gagel and Czembirek report the case of a man aged 38 who was operated on for a perforated ulcer of the stomach. Local anesthesia was used on the abdominal wall (300 cc. of 0.75 per cent tetracaine hydrochloride and 1 cc. of 1 per cent epinephrine hydrochloride). Gastric resection and gastrojejunostomy were performed. The presence of a peptic ulcer was confirmed microscopically. The drain was removed in four days, with no change in the skin. Eight days later there was a discharge from the site of the drain, and in another eight days an area of necrosis of the skin the size of a 5 mark piece was noted. The necrotic area spread. There was a purulent discharge from the edges of this cutaneous defect. The necrosis involved only skin, subcutaneous tissues and fascia; the muscle was not affected. Neurologic examination revealed nothing abnormal. The patient died about two months after operation, of pneumonia.

That the unusual condition described by the authors was not due to the local anesthesia is evidenced by the eight day interval between the operation and the first indication of necrosis. The clinical picture was not that of a spreading infection of the abdominal wall. Histologic study of the cord revealed changes which may explain the necrosis of the abdominal wall. Localized gliosis was found in the sixth, seventh, eighth and ninth thoracic segments; this change involved especially the so-called intermediary zone of the anterior horn cell region. The cells in this region showed evidence of chronic degeneration. The authors conclude that these anatomic observations point to the probability that this intermediate zone is a trophic center. There is insufficient evidence to indicate that the changes in the cord were responsible for the appearance of the peptic ulcer.

SAVITSKY, New York.

Psychiatry and Psychopathology

AN UNUSUAL COMPLICATION OF CONVULSIVE THERAPY. H. H. HAINES, Psychiatric Quart. **18**:273 (April) 1944.

Haines reports a case of bilateral fracture of the acetabulum in a 17 year old patient with schizophrenia following the second electric shock treatment. The boy had also had three spontaneous convulsions in the three years prior to therapy. A roentgenogram of the pelvis after shock showed deep acetabular notches on each side, with no displacement of the cracked thin fragments. The lesions healed with rest and left limitation of motion in adduction and flexion. The patient could walk and sit fairly well.

The type of pelvis seen in this patient was first described by Otto in 1824; it has been thought by some authors to be congenital and by others to be the result of chronic disease. The etiologic factors in this case remain uncertain.

MCCARTER, Boston.

THE PSYCHOLOGY OF OBSTINACY. CHRISTINE OLDEN, Psychoanalyt. Quart. **12**:240, 1943.

Olden points out that stubbornness originally meant heroism and that psychologically obstinacy is a way of fighting to establish supremacy. In childhood it

is a means of combating the threats imposed by the environment; later it is used to combat the threats of the superego.

Obstinacy is a protection against feelings of guilt and fear and is a means of combating anxiety, especially anxiety rooted in feelings of inferiority and humiliation. It enhances the feeling of omnipotence whenever self esteem is threatened by some real object or by the superego, since self esteem is unstable in obstinate people. Obstinacy is a function of the ego which develops during the anal period, for obstinacy is holding back for the purpose of opposing; but it also has an oral root in the baby's screaming when he wants to enforce his will.

Passive obstinacy is a compromise between aggressive feelings and anxiety. It is a good method of bolstering the self esteem but fails because it produces secondary guilt feelings and because it often conflicts with reality.

The analyst's attitude is important in analyzing obstinate patients. He should not meet obstinacy with counterobstinacy. He can help the patient by strengthening his ego through freeing him of his fears of the analyst. He can help by confronting the obstinate attitude with reality. He can increase the patient's self esteem by praising his efforts.

PEARSON, Philadelphia.

THE CONCEPTION OF THE REPETITION COMPULSION. EDWARD BIBRING, Psychoanalyt. Quart. **12**:486, 1943.

The concept of the repetition compulsion is a complex one and has at least two aspects: 1. The repetition compulsion is the expression of the inertia of living matter, of the conservative trend toward maintaining and repeating intensive experiences. 2. It is a regulating mechanism, with the task of discharging, in fractional amounts, tensions caused by traumatic experiences after they have been bound.

The two meanings are not identical. The first meaning may be called a restitutive tendency and the second a repetitive, or reproductive, tendency. Freud used the term "repetition compulsion" to cover both meanings, sometimes referring to one and sometimes to the other. He attributed acting out in analysis and in life to the repetitive tendency, whereas he used the concept of the restitutive tendency as evidence supporting the assumption of two types of primal instincts. However, he used only the restitutive tendency of the repetition compulsion to characterize the life instincts, and not at all the repetitive tendency. This definition leads to a contradiction as to what are life instincts and what are death instincts. Freud regarded the repetition compulsion as a regulating mechanism which helps the psychic apparatus either to discharge incoming stimuli completely or to reduce them to the lowest possible level. This concept, however, divides the repetition compulsion into the automatic process of binding because of the need for protection against intensive stimulation and the consequent mechanical trend toward abreaction of the accumulated tensions. This does not seem satisfactory and raises the following questions: What is the nature of the conservative principle, with its repetitive and restitutive tendencies? What is the relation of these tendencies to each other? Is the restitutive tendency only a special instance of the mechanical trend toward discharge of bound energies, or is it an active tendency?

The repetition compulsion may be defined as the tendency toward automatic or impulsive repetition, and eventually discharge, of painful (traumatic) experiences. This definition gives certain criteria: the automatic or impulsive nature of the repetition; the painful character of what is repeated. (These two criteria correspond solely to the repetitive tendency.) There is a kind of spontaneity; i. e., the repetition will occur for internal reasons only; there will be a decrease of the intensity of the tensions. (These two criteria correspond to the restitutive tendency.)

Hartmann has given the most complete enumeration of the various kinds of repetitions. According to him, repetition occurs "(1) in response to the same stimuli; (2) when what was experienced resulted in pleasure . . . or was pleasurable in itself; (3) in connection with automatisms of thought and action: (4) when interested actions were not completed; (5) when traumatic experiences

have not been assimilated. The last-mentioned example corresponds to the repetition compulsion.

From clinical examples the author shows that the restitutive tendency is a function of the ego while the repetitive tendency is a function of the id. The restitutive tendency is not a defense mechanism of the ego, however, but is part of the working off of mechanisms of the ego the function of which is to dissolve the tension gradually by changing the internal conditions which give rise to it. They are not abreactions, although abreaction in small doses may take place during the process.

The ego tends to try to manage the repetition compulsion. If the repression which brings the repetition compulsion into play ceases to exist, the ego is called on to deal with the relaxation of the repetition compulsion and the new formation of the instinct through detachment of the libido or through compensation and adaptation through familiarity. If the repression remains, the ego may be weaker than the repetition compulsion and may be completely dominated by it. Or the ego may be stronger and may deal with the repetition compulsion actively by absorbing it, as in the case of destiny neuroses. The real problem is the relation of the repetition compulsion to the pleasure principle.

Freud assumed that instincts clung to primary or intense experiences and followed the way paved by these experiences irrespective of pleasure or pain. He considered this a fundamental characteristic of instinctual drives. The repetition compulsion is an instinctual automatism. There is no fundamental difference between fixation and repetition compulsion except that a fixation is the link between an instinctual drive and pleasurable experiences, while the repetition compulsion is the result of a link between instinctual drives and any intense experiences, whether pleasurable or not.

The repetition compulsion is beyond the pleasure principle but is not absolutely opposed to it. It exists prior to the pleasure principle, and it is broader, since it can fix both the pleasurable and the painful. Once the repetition of the painful has been accepted as beyond the pleasure principle, it can easily be seen that the ego secondarily may use this repetition to obtain pleasure.

PEARSON, Philadelphia.

SELF PRESERVATION AND THE DEATH INSTINCT. ERNST SIMMEL, Psychoanalyt. Quart. **13**:160, 1944.

Simmel attempts to advance another theory concerning the dualistic theory of instincts, which differs to a certain extent from Freud's views. Freud's theory of instincts was always based on one principle, that of dualism reflecting the dynamics of two instinctual and opposing energies. His first concept was that of a conflict between self preservation and sexuality. His final concept was that of an instinctual conflict within the ego, a struggle of one part of the ego, which desires to keep alive, against another part, which desires to destroy itself.

Simmel's theory substantiates Freud's view that the fundamental conflict which binds and disrupts extraindividual life is also responsible for all intraindividual disturbances, i. e., an internal conflict between constructive and destructive principles, a conflict between love and hate. He considers the destructive energies to be manifestations not of a death instinct but of the instinct of self preservation. This makes the need for self preservation a libidinal component of the ego and constitutes an apparent contradiction in ascribing destructive tendencies to it, for libido is supposed to bind substances, not to aim at their disruption and destruction.

There is no contradiction, however, if the development of Freud's theories of libido and instinct are reviewed, particularly the modifications of the original theory which were necessary when the concept of narcissism was introduced. This made the previous qualitative prerequisite for sexual libido, the provision of organ pleasure, lose its significance. It was replaced by the view of a quantitative distribution of narcissistic libido within the ego. The original concept of the pleasure-pain principle—i. e., to provide pleasure and to avoid pain—was enlarged into the

concept of a principle which tended to keep libidinal tension within the ego below the level where pain was experienced. When this did not occur, i. e., when there was a quantitative disturbance in the equilibrium of narcissistic libido, anxiety developed. Self preservation is an attempt to preserve the coherence of the structual unity of the ego by means of an adequate distribution of narcissistic libido; i. e., it is the ego's tendency to keep itself free from anxiety.

Self destruction is a cardinal principle in nature, but it shows only one of the characteristics of an instinct, the aim of removing excitation. Self preservation has all the characteristics of an instinct. Its origin lies in the instinct to devour. Its organic source is the gastrointestinal tract. Its aim is to remove stimuli from the gastrointestinal tract, and its object is food. Its ultimate aim in the deep unconscious is that of self preservation and self development, in contrast to the ultimate aim of the sex instinct, i. e., reproduction.

Freud defined libido as energy aiming at the synthesis of living substances, and even the apparent destructive energy of the instinct of self preservation fits this definition and so places it in the category of libidinal energies. It seeks to achieve this aim simply within the individual, while the sex instinct seeks to achieve the aim outside the individual. The gratificaton of the sex instinct removes the excitation and retains the object. The gratification of the instinct of self preservation removes the excitation and destroys the object. The instinct of self preservations aims at the reinstatement of the equilibrium of narcissistic libido. It aims primarily at reinstating as much as possible complete instinct repose. This condition is only maturing from the primitive object relation, governed by hate, to the civilized object relation, governed by love.

Nirvana is the basic attraction of all progressive trends which constitute mental disorders. Rank was correct in his view of the significance of the trauma of birth for the genesis of the neuroses, but he failed in his interpretation. One does not want to repeat the trauma of birth, but one has to repeat the aggressive alimentary act by which one was able to annul that trauma.

In the psychoses the ego abandons genital primacy and gives in to the gastrointestinal primacy. In the transference neuroses the ego is arrested on the way to its ultimate aim of regression by stages of libidinal object fixation, where there already exists a fusion of immature sexual libido with gastrointestinal libido. Neuroses and psychoses reflect a defense by the ego against the dangerous consequences of regressively awakened destructive devouring tendencies. Basically, the ego is caught between two attractions, that of preserving the frustrating object and that of preserving the narcissistic equilibrium. In the transference neuroses it decides in favor of the object; in the psychoses, in favor of instinct repose.

Simmel's theory may be summarized as follows:

There is a devouring instinct in man which is closely associated with the need for self preservation. The process of identification which ends the Oedipus conflict substitutes for and wards off incorporation, which is the result of the ego's regression to the primacy of the gastrointestinal instinct. Failures in this process precipitate a morbid psychopathologic state, which turns self preservation into self destruction by subjecting the ego to the attracting power of the Nirvana principle.

PEARSON, Philadelphia.

PSYCHOSURGERY: AN EVALUATION OF TWO HUNDRED CASES OVER SEVEN YEARS. WALTER FREEMAN and JAMES WATTS, J. Ment. Sc. **90**:532 (April) 1944.

Freeman and Watts first describe the technic of their operation. Different patients require the severing of different amounts of white matter: Patients with schizophrenia and obsessional neuroses of long standing require more extensive cuts than patients with pure affective psychoses. About 20 per cent of their patients have required a second operation, and some have required a third. The performance of a second operation may cause considerable inertia and incontinence. It may be done any time after the first. If the patient does not show the inertia and dis-

orientation anticipated, or if the incisions are shown by roentgenographic examination to be poorly placed (iodized oil is placed in the incision to make the tract visible), the incisions may be repeated in a few days.

The authors find that the two chief features in the two weeks following lobotomy are indolence and lack of tact. The patients are apt to show euphoria or exuberance but with petulance on being thwarted. There is distractability and no desire for perfection. But in the course of months or years improvement sets in. Some patients continue to improve five years after operation. Some are said to be even more productive than ever in their lives.

Of 154 living patients operated on at least six months previously, 61 per cent were usefully occupied, and only 12 per cent had to be confined to institutions. The patients with severe emotional tension have done best and the alcoholic patients worst.

Autopsy of 8 postlobotomy brains has shown cystlike cavities beneath small cortical incisions. The cortex at the frontal pole shows no demonstrable change. "There are some degenerated fibers (Marchi) anterior to the lesions, particularly in the upper quadrant. The most striking alteration is the severe degeneration of the nucleus medialis dorsalis of the thalamus. Here the cells in the lateral portion of the nucleus have undergone a reduction of 75 per cent or more with some shrinkage of the nucleus as a whole and a little reactive gliosis. The pathologic findings indicate the thalamofrontal radiation has been fairly completely severed. . . . Whether this is the only pathway of importance in the operation of prefrontal lobotomy has not been determined, since rather restricted incisions aimed at the fasciculus cinguli have also produced striking alterations in the patient's behavior, but more particularly along the lines of autonomic alterations."

In summary, the authors believe "that prefrontal lobotomy abolishes many of the symptoms of mental disorder by bleaching the affect attached to the ego. Symptoms such as anxiety, worry, apprehension, obsessive thinking and the like are prominent in most of the psychoses at least during their inception. These symptoms have the egocentric signature. The threat to the security and integrity of the individual is magnified by himself. By reducing the emotion expended upon the ideas relating to the self, prefrontal lobotomy reduces the significance of the self to the self and tends to abolish egocentricity."

McCarter, Boston.

Neurosis and Intelligence. H. J. Eysenck, Lancet **2**:362 (Sept. 18) 1943.

Eysenck studied the relation of neuroses to intelligence as measured by the results of the progressive matrix test on about 3,000 neurotic men and women. Of these subjects, a little less than 500 were women, for whom it is said that the test has not been as well standardized as for men. Over 3,000 male army recruits were used as controls. The outstanding finding was the absence of a difference in the average intelligence levels of the neurotic subjects and the controls. The nearest thing to a difference between the normal and the neurotic subjects was the fact that a larger number of neurotic subjects showed an intelligence level which could be classified as a little above or a little below the average for the test, whereas a greater number of normal subjects were rated as of average intelligence.

The author believes that his observations support the view expressed by others that the so-called lower intelligence of neurotic persons is caused by a weakness in the efficiency of mental functioning rather than by their inability to abstract and reason.

McCarter, Boston.

MYXOEDEMA AND PSYCHOSIS. H. ZONDEK and G. WOLFSON, Lancet **2**:438 (Sept. 30) 1944.

Zondek and Wolfson report the case of a previously healthy woman of 23 in whom all the signs of myxedema developed after delivery of a normal, healthy child. The most striking feature was the development of true schizophrenia, for which she was admitted to a mental disease hospital eighteen months after delivery and treated, with little improvement, with insulin and electric shock.

At the end of the eighteen months she was given Thyroidin, 0.2 Gm. four times a day, and by the fourth day her urinary excretion had risen from 1,000 to 2,700 cc. The psychosis was better in this short time and cleared in a fortnight. There was no change in the basal metabolic rate at the time the mental change was first evident; of the objective signs, only the urinary output altered. Her voice was clearer, the reflexes were more active and the palpebral fissures wider by the end of the first fortnight. A year later she was still physically and mentally well and was still receiving 0.2 Gm. of Thyroidin daily in alternate weeks.

The authors believe that the favorable effect of the drug was due to dehydration of the cerebral tissue.

McCARTER, Boston.

PSYCHOTIC EPISODES IN PSYCHOPATHIC PERSONALITIES. EDUARDO BRÜCHER ENCINA, Rev. de psiquiat. y disc. conexas **9**:128, 1944.

The author reports on the occurrence of psychotic episodes in patients with psychopathic personalities in a hospital in Chile during the period from 1941-1943, inclusive. There were 61 patients with psychopathic personality among 4,631 admissions during the three years (1.3 per cent); 44 were men and 17 women. Forty-nine (80.3 per cent) were discharged; 25 recovered; the condition of 16 was improved, and 8 showed no improvement. Paranoid types, perverts, amoral psychopaths, unstable personalities and patients with hyperthymic syndromes predominated. The author notes excitement, depression and schizoid and delirium-like reactions among the types of psychotic episodes seen in this group. He believes that the concept of psychopathic personality has a sound basis and is clinically valuable.

SAVITSKY, New York.

Meninges and Blood Vessels

MENINGITIS IN CHILDREN. CHARLES H. HOLLIS and JAMES MARVIN BATY, New England J. Med. **230**:278 (March 9) 1944.

Hollis and Baty report their observations in 28 consecutive cases of meningitis in children. There were 9 children with influenzal meningitis, 12 with meningococcic meningitis, 5 with pneumococcic meningitis, 1 with meningitis due to the colon bacillus and 1 with meningitis due to infection with Salmonella. All but 3 of the patients were less than 3½ years of age.

The authors conclude that combined treatment with specific antiserum and a sulfonamide compound is advisable in cases of influenzal and pneumococcic meningitis. In treatment of meningococcic meningitis sulfonamide therapy is adequate except in cases of fulminating meningococcic infection.

The therapeutic results were as follows: Two patients of the 9 with influenzal meningitis and 2 of the 12 with meningococcic infection died; both of these were infants with acute meningococcemia and presented the Waterhouse-Friderichsen syndrome. Four patients out of the 5 with pneumococcic meningitis died. All were under 8 months of age. The infant with colon bacillus meningitis survived, after

a course of treatment with sulfathiazole, but blindness and atrophy of the optic nerve resulted. The infant with meningitis due to Salmonella oranienburg did not respond to sulfathiazole and died.

GUTTMAN, Philadelphia.

CAUSALGIA AND GANGRENE: RARE COMPLICATIONS IN MENINGOCOCCAL MENINGITIS. PHINEAS BERNSTEIN, New England J. Med. **230**:482 (April 20) 1944.

Bernstein reports the case of a 34 year old woman with meningococcic meningitis, for which she was successfully treated with sulfadiazine, who later had gangrene of several toes and areas of the skin and causalgia of the right upper extremity. The causalgia disappeared about three and a half months after the onset of the illness.

GUTTMAN, Philadelphia.

Diseases of the Brain

SUBACUTE DEGENERATION OF THE BRAIN IN PERNICIOUS ANEMIA. RAYMOND D. ADAMS and CHARLES S. KUBIK, New England J. Med. **231**:1 (July 6) 1944.

Adams and Kubik report their observations on 2 patients with pernicious anemia who not only had evidence of involvement of the posterolateral column but exhibited psychiatric symptoms. One patient had "acted queerly for several weeks" prior to admission and subsequently lapsed into a stupor and died. The other patient had a history of being "vague as to details of her illness and was irritable and difficult to manage."

The pathologic changes in the brain and spinal cord in both patients were almost identical. The important anatomic changes consisted of a diffuse, uneven degeneration of nerve fibers in the spinal cord and the cerebral white matter, with relatively little proliferation of fibrous glia. The lesions in the brain resembled those in the spinal cord so closely that there could be little doubt concerning their identity.

The authors favor the supposition that both subacute combined degeneration of the spinal cord and subacute degeneration of the brain represent an advanced stage in a specific process that is induced by a deficiency of certain substances necessary for the metabolism of myelinated nerve fibers. Also, they state that it is not to be expected that every patient with pernicious anemia will have demonstrable cerebral lesions, but all those in whom there are definite and widely disseminated cerebral lesions will probably have mental disorders.

GUTTMAN, Philadelphia.

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF POLYCYTHEMIA VERA. W. S. TINNEY, B. E. HALL and H. Z. GRIFFIN, Proc. Staff Meet. Mayo Clinic **18**:300 (Aug. 25) 1943.

Tinney, Hall and Griffin report a number of cases of polycythemia vera in which difficulties referable to the central nervous system were manifest.

They first mention symptoms and signs reported by other observers in cases of this disease. Impaired memory, lethargy, depression and delusions, tinnitus, apprehension, psychoses, insomnia, excitability, epilepsy, aphasia and cerebral thrombosis or hemorrhage have all been mentioned. Headache, scotomas, paresthesias and vertigo have also been found. Focal localizing signs have sometimes been so prominent that operation for cerebral tumor has been performed. Symptoms referable to the nervous system have seemed to point to a functional disorder. Sometimes mental deterioration or paralyses have been present.

The authors found symptoms referable to the nervous system in 127 of their 163 cases of polycythemia vera. Headache was the most frequent symptom and

was not characteristic in location though most often generalized. The following tabulation summarizes the manifestations of the disease referable to the central nervous system, with their distribution in the present series:

Symptoms	No. of Cases
Headache	59
Vertigo	52
Weakness and fatigue	41
Nervousness	29
Visual disturbances	28
Severe neuroses with exhaustion	27
Paresthesias	23
Aphasia	13
Loss of consciousness	10
Tinnitus	8
Mental depression	7
Complications	
Cerebral thrombosis	27
Suspected cerebral tumor	8
Choked disk	4
Herpes	1
Combined sclerosis	1

The authors point out that objective neurologic signs were found in 17 per cent of their cases. Objective signs were of progressive nature in 8 cases, so that cerebral tumor was suspected. They state that when there is uncertainty as to which entity is causing the cerebral signs—polycythemia or tumor—treatment for the former should be tried first. The reduction in blood volume should result in lessening of signs of involvement of the nervous system unless there is permanent injury following thrombosis or hemorrhage. Progression of symptoms should lead to suspicion of a mass-expanding lesion.

McCARTER, Philadelphia.

OBSERVATIONS ON THE TOE FLEXOR (SCHRIJVER-BERNHARD) AND TOE-FANNING REFLEXES. H. H. FLEISCHHACKER, J. Ment. Sc. **89**:403 (July-Oct.) 1943.

Fleischhacker discusses the Schrijver-Bernhard reflex and the toe-fanning phenomenon. The former is elicited by tapping with a percussion hammer over the tibia or the adjacent muscles. A plantar flexion of the small toes is considered a positive reaction. The toe-fanning phenomenon is elicited by applying "the now usual technique for testing Oppenheim's reflex, which is somewhat different from that originally used by Oppenheim. Care should be taken to exert pressure only on the skin not on the tibial muscles."

The author found these reflexes to be five or six times as frequent in patients with catatonic schizophrenia as in patients with other mental disorders of functional type. They occur at least as often as "the usual psychomotor symptoms (catalepsy, pulling, resisting—taken together). It may be claimed therefore that the phenomena are of a differential diagnostic value. The S. B. reflex is characteristic for a certain type of subcortical extrapyramidal disorganization, while the fanning phenomenon is apparently released by cortical disturbances."

In a group of normal controls, under conditions of muscular contraction assumed in order to simulate catatonia, there were a number of positive responses, but a true Babinski sign was not elicited.

The author also found that the two reflexes described predominated on the left side in a majority of the catatonic patients.

McCARTER, Boston.

Diseases of the Spinal Cord

POLIOMYELITIS ON THE ISTHMUS OF PANAMA. CARL E. TAYLOR, New England J. Med. **230**:790 (June 29) 1944.

Taylor reports observations in 72 cases of anterior poliomyelitis in the Gorgas Hospital, Canal Zone, over a thirty-eight year period, from 1904 to 1942. The average incidence was 1 case of poliomyelitis in about 7,000 admissions to the hospital. Eight hospital cases were not included in the study group because they failed to meet the rigid diagnostic standards or because the infection had not been contracted on the isthmus.

Taylor noted that the crest of the seasonal curve occurs during November, December and January—the end of the rainy season. Most of the patients resided in urban areas. Poliomyelitis was about three times as common in white persons as in Negroes. Of the white persons, 52 per cent were 5 years of age or under, as compared with 85 per cent of the West Indian Negroes and 83 per cent of the Panamanians. There were twice as many males as females among the white patients and the Panamanians, but the incidence in the two sexes was equal among the West Indian Negroes.

GUTTMAN, Philadelphia.

Peripheral and Cranial Nerves

THE RAMSAY HUNT SYNDROME. NORMAN R. SHULACK and MILTON H. KIBBE, J. Nerv. & Ment. Dis. **101**:9 (Jan.) 1945.

The syndrome of herpes zoster auricularis with facial palsy and auditory symptoms was first described by Ramsay Hunt in 1907 and has been infrequently reported since. The authors describe the case of a 27 year old soldier who was hospitalized because of vertigo, inability to close the right eye and pain in the right ear. Examination revealed right-sided facial palsy of peripheral type, redness of the right concha, nerve deafness in the right ear, hypalgesia and hypesthesia of the right side of the face and absence of the right corneal reflex. The next day a herpetic eruption appeared on the concave surface of the right concha. Spinal tap on the eleventh day revealed that the fluid was under normal pressure, with a count of 44 cells per cubic millimeter, of which 95 per cent were lymphocytes. Improvement was progressive, and by the thirty-fourth day the patient had completely recovered.

The authors believe that this case lends support to the view that herpes zoster is a trophic expression of fairly localized inflammation of the central nervous system.

CHODOFF, Langley Field, Va.

LOCALIZED NEURITIS OF THE SHOULDER GIRDLE. J. D. SPILLANE, Lancet **2**:532 (Oct. 30) 1943.

According to Spillane, cases with unusual neuritic features have come to be recognized in the armed forces which were not observed before the war in such numbers. The author himself has seen 20 such cases, and he has studied the records of others. A fairly clear clinical picture has emerged of what may be called localized neuritis of the shoulder girdle. In 42 of these 46 cases the onset of the illness was characterized by sharp pain about the shoulder. The painful sites were usually along the upper border of the trapezius muscle and over the spinatus muscles and the belly of the deltoid muscle. Pain was sometimes felt along the inner border of the scapula, in the axilla or up the side of the neck. Many patients said it was severe and burning, and nearly all of them needed analgesics. The pain was commonly worse at night and disturbed or prevented sleep. It was aggravated by the patient's lying on the affected side and persisted acutely for from three to fourteen days; thereafter it rapidly subsided, but in a few cases a chronic ache was complained of for six or seven weeks. The pressure of braces or the weight of a gun

or pack aggravated the discomfort. Pain was more severe in the muscles which subsequently showed atrophy. The muscles affected were the serratus magnus, spinatus, deltoid, trapezius, sternocleidomastoid and rhomboid. Effective movements of the shoulder girdle were greatly hampered. The wasted deltoid muscle, with paralysis of abduction, the hollowed supraspinous and infraspinous fossae of the scapula and the winging of the scapula, alone or in various combinations, produced a striking deformity of the shoulder girdle. The usual forms of treatment for neuritis did not seem to alter the course of the illness. If a patient with this condition is seen for the first time some months after the acute phase, the malady may be mistaken for poliomyelitis. The author differentiates the condition from poliomyelitis, acute brachial radiculitis and neuritis. He considers the possible role of "injection neuritis" and of repeated minor traumas. The preponderance of cases of right-sided neuritis and the selective nature of the muscle wasting suggest that "injection neuritis" is not an important factor. It is quite possible that the long thoracic and suprascapular nerves could be injured by carrying a weight (pack and rifle) across the shoulder. Many of the patients, however, were employed in sedentary posts, and in 26 of them the illness developed during convalescence in hospital.

J. A. M. A.

Treatment, Neurosurgery

TREATMENT OF NARCOLEPSY WITH DESOXYEPHEDRINE HYDROCHLORIDE. L. M. EATON, Proc. Staff Meet., Mayo Clin. **18**:262 (July 28) 1943.

Eaton found that of 15 patients with the chief complaint of narcolepsy, 12 showed subjective improvement with the use of desoxyephedrine hydrochloride, and he expressed preference for this drug to amphetamine, tried previously. Desoxyephedrine hydrochloride was given in 2.5 mg. tablets in the morning, at noon and at 4 p. m. With 3 patients the last dose was omitted because it produced insomnia. None of the patients was bothered by other untoward effects of the drug. Two patients preferred amphetamine. Evaluation of the response was based entirely on letters from the patients. Patients showed improvement over periods of six to seventeen months.

McCARTER, Boston.

USE OF THE RESPIRATOR IN TREATMENT OF BARBITURATE INTOXICATION. MANUEL FALCÓN G., Arch. de neurol. y psiquiat. de México **6**:299 (Sept.-Oct.) 1943.

The author suggests artificial respiration in an "iron lung" for patients with severe barbiturate intoxication which fails to respond to strychnine, coramine or picrotoxin. Bulbar symptoms are often the cause of death. Respiration is often seriously defective. The author reports only 1 case, that of a woman aged 26, who was desperately ill when placed in the respirator. She was pulseless and unconscious; the blood pressure was not obtainable, and she had corneal areflexia and evidence of anoxemia. In thirty hours after being placed in the respirator she was able to breathe by herself; after forty-eight hours she regained consciousness, and after five days she was transferred home. Unfortunately, pneumonia developed, and she died forty-eight hours after leaving the hospital. In spite of the tragic outcome in this case, the author recommends use of the respirator in cases of severe and desperate barbiturate intoxication.

SAVITSKY, New York.

Congenital Anomalies

UNUSUAL CONGENITAL ANOMALIES OF THE LUMBO-SACRAL SPINE (SPINA BIFIDA). J. M. MEREDITH, J. Nerv. & Ment. Dis. **99**:115 (Feb.) 1944.

Meredith reports 3 unusual cases of spina bifida. The first was that of a 6 year old girl previously treated for an infection of the urinary tract who proved to have a complete spina bifida (occulta) throughout the entire lumbar portion of the spine

and the sacrum. At operation large portions of the posterior bony canal below the twelfth thoracic and the first lumbar vertebra were observed to be absent, and the terminal roots of the cauda equina were gathered together in a cable of nerves, which extended along the sacrum posteriorly to a dimple in the skin just above the gluteal cleft. This was released, affording relief of tension on the cauda equina. The operation resulted in considerable improvement in the patient's sphincter control. This case illustrates the results of abnormal fixation of the cord or cauda equina in precluding the rostral migration which normally occurs with the lengthening of the spine.

The second case was that of a 22 year old man with weakness and atrophy of the left leg, saddle and genital anesthesia and marked bladder disability, in which roentgenograms revealed a pronounced congenital deformity of the sacrum. At operation the conus medullaris was found to be adherent to the inner dura at the level of the second bony segment of the sacrum on the left; it was surrounded by a large pad of fat. Partial freeing of the conus relieved tension on the cord and resulted in considerable postoperative improvement.

The third case was that of a 13 year old girl who had had a simple lumbosacral meningocele repaired at the age of 3 years, with excellent results and entire absence of symptoms until three months before the present admission, when severe pain in the legs and slight dysuria developed. There was a complete spinal fluid block, and myelographic examination with iodized poppyseed oil revealed a mass lesion at the level of the third lumbar vertebra, which after operative removal proved to be a large cholesteatoma. Postoperative recovery was complete. The author believes this combination of a large congenital tumor and a simple meningocele to be unique.

CHODOFF, Langley Field, Va.

News and Comment

COURSE IN RORSCHACH TEST, MICHAEL REESE HOSPITAL

The Division of Neuropsychiatry, Michael Reese Hospital, announces its 1946 course in the Rorschach test, to be conducted June 3 to 7, inclusive, by S. J. Beck, Ph.D. The teaching this year will focus especially on the more severe neurotic conditions. The Rorschach records to be demonstrated will therefore be those derived from patients in acute conflict, including veterans of the war. For information, write to the secretary, Division of Neuropsychiatry, Michael Reese Hospital, Twenty-Ninth Street and Ellis Avenue, Chicago 16.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

HAROLD G. WOLFF, M.D.,

Chairman, Section of Neurology and Psychiatry, in the Chair

Combined Meeting, Feb. 13, 1945

Electroencephalographic Changes Associated with Psychopathic Personalities. DR. OSKAR DIETHELM and DR. DONALD J. SIMONS.

The well person is self dependent; he recognizes the need to adapt to life around him and is able to do so. Abnormalities of behavior designated by the term "psychopathic" may affect a person's self dependence or his relationship to his environment, and very often both. In the past, these behavior disorders have been considered from the point of view of their relation to the well known forms of psychoses. Other groupings have been formed on the basis of the type of difficulties which were most obvious. In this presentation we shall classify psychopathic personalities according to the disturbance of function of the personality. From a psychopathologic point of view, one may find disturbances of the organization of the personality or an exaggeration or underdevelopment of various groupings of personality features. Psychopathic personalities, in which the organization of the personality is primarily disturbed, may be due to late maturing, i. e., psychologic immaturity as compared with the chronologic age. Another disorder, frequently related to immaturity, is characterized by looseness of organization of the whole personality, thus permitting contradictory strivings and acts. Its opposite is expressed in loss of plasticity, as seen in the rigid personality. Examples of psychopathic maladjustment based on exaggeration of various personality features are found in the excessively moody, the poorly adjusted socially or the poorly adjusted ethically. It is also important to evaluate the genetic and dynamic factors. In some psychopathic personalities constitutional factors predominate. In others, psychoneurotic and other psychodynamic factors prevail.

From a study of all patients with psychopathic personalities admitted to the Payne Whitney Psychiatric Clinic in the last two years the following patterns emerged: 1. Definite psychoneurotic type. The psychoneurotic reactions may have had their recognizable onset in childhood, in adolescence or in early adult life, but they resulted in such a degree of social maladjustment that the diagnosis of psychopathic personality seemed indicated.

2. Cyclothymic type. Patients with this type showed maladjustment because of pronounced and easily provoked mood swings. These patients often utilized psychoneurotic factors.

3. Persons with poor ethical standards and resulting social difficulties. The patients showed irresponsibility, with disregard for consequences, lack of persistence of emotional relationships and absence of emotional depth. The symptoms were stealing, untruthfulness, truancy and irresponsibility toward debts.

4. Loose organization of the personality and immaturity. The patients were characterized by unsatisfactory emotional control, contradictory strivings, poor self discipline and frequently a rebellious attitude toward authority and society. The patients were of the aggressive, as well as the passive, type.

5. A generally inadequate personality with vague thinking. Some of the patients had high ethical standards; others, unusually low. They were of the aggressive as well as of the passive type.

The 61 patients in this study were tested in the course of routine electroencephalographic examinations. Interpretations were made without knowledge of the clinical picture or the diagnosis. Records were made on a two channel ink-writing oscillograph of the Grass type. Some of the patients were given 100 Gm. of dextrose by mouth before the test was made in order to eliminate the possible occurrence of slow waves due to low blood sugar. In a few cases the blood sugar level was determined, and the results led us to believe that all the patients had a blood sugar level above 100 mg. per hundred cubic centimeters at the time of the test.

Forty-nine per cent of the patients in this series had abnormal records. The psychoneurotic and cyclothymic groups showed normal records. The abnormal electroencephalograms, which were confined to the other three groups, may be divided into four types: records showing low voltage fast activity, records showing 5 to 7 a second activity, records showing low voltage slow activity and miscellaneous abnormal or doubtful records. In the group of patients with poor ethical standards, moderately slow, 5 to 7 a second, activity was the predominating abnormality (58 per cent). The group characterized by immaturity and poor emotional control had poorly defined electroencephalographic records. The records for the group of inadequate personalities were made up primarily of low voltage slow activity (64 per cent of the record).

Since no type of abnormality is absolutely characteristic of one type of psychopathic personality, it is not possible to make a diagnosis from the record. Further, we do not claim that all records showing low voltage fast, low voltage slow or 5 to 7 a second activity are those of psychopathic personalities. This point has not been studied.

Since neurologic examination of all our patients revealed no defects, and since the patterns differ to a striking degree from those seen in cases of structural disease of the brain, we believe that there is no evidence of structural changes. Therefore we infer that some types of psychopathic personality have a defect in the physiologic functioning of the brain.

DISCUSSION

DR. BERNARD L. PACELLA: The paper by Drs. Diethelm and Simons presents some fascinating and important observations. An impressive aspect of the presentation concerns the method of subdividing the psychopathic groups into categories which appear to be scientifically valid for purposes of laboratory investigation. In contrast to what has been presented here, the literature contains much electroencephalographic investigation of psychiatric disorders in which the clinical groupings are not clearly defined for purposes of careful laboratory study. For this reason, controversy prevails regarding the incidence of abnormal tracings in different psychiatric disorders.

It is of interest that the patients with psychopathic personalities of the psychoneurotic and cyclothymic types all exhibited normal electroencephalograms, whereas those with poor ethical standards, exhibiting a lack of persistence in emotional relationships, lack of emotional depth and aggressive or antisocial behavior, all had abnormal electroencephalograms. This striking difference in electroencephalographic patterns between two such types of psychopathic personalities is almost startling. Of course it is open to question whether all persons who could be classified in either category would maintain the 100 per cent normal or abnormal record, and I am quite certain that the authors themselves would not necessarily anticipate such a finding if they had much larger groups for study. However, even if these figures were extended in some degree by the addition of more subjects in the group under investigation, I doubt whether the significance or implications of the observations presented this evening would be altered.

It should be kept in mind that the electroencephalogram is essentially a silhouette, or a summation, of cerebral electrical activity, which, in turn, is intimately related to the physiologic activity and the functioning of the brain.

It is likely, therefore, that a disturbance in the physiologic or functional organization of the brain which might be manifested in an abnormal electroencephalogram may also be manifested in abnormal behavior of the organism. Just as there are grades of anatomic anomalies and congenital histologic disturbances in the brain which may be associated with deviate behavior, so there may be grades of functional anomalies and constitutional physiologic disturbances also associated with certain types of abnormal behavior which may be revealed by a finer technic, such as the recording of the electroencephalogram.

The question may arise whether environmental factors which impose continued stress or provide for faulty development of the personality functions may produce a disturbance in cerebral physiologic activity which could be reflected in the electroencephalogram. Although my colleagues and I have a few cases in which this seems a likely possibility, our observations indicate that it is far more probable that in the great majority of instances a faulty constitutional cerebral organization has been the originally important factor as a determinant, or at least a concomitant, of the disturbance in behavior.

This statistical presentation of the electroencephalographic abnormalities is in essential conformity with the observations of other investigators and tends to support some of our own studies on delinquent children. It might be of interest here to note that patients who have a history of psychopathy in members of the family are more likely to show abnormal records than are other persons.

Certain questions arise which are not mentioned in the paper, although I am sure they must have been considered by the authors. First: Were patients excluded from this study if they had previously been subjected to severe head trauma or had had encephalitis or were blood relatives of epileptic persons? Were any of the patients receiving barbiturates or other medicaments which might conceivably have produced an effect on the electroencephalogram? I should be interested in knowing also whether the abnormal features were of diffuse nature over the entire cortex or whether they were more prominent in some particular region of the brain. Both phylogenetically and ontogenetically the frontal cortex appears to be the last to develop and to become organized physiologically in the brain, and I wonder whether the abnormal activity might not generally be more prominent or more frequent over the anterior aspects of the cerebral hemispheres. This, I may say, has been our experience in patients of the psychopathic types under discussion.

Dr. Donald J. Simons: No patient having convulsions was included in this group. No patient with a recent head injury was included. I do not believe that any of the patients were receiving barbiturates at the time of the test. Abnormalities were most prominent in the frontal and parietal regions. In some patients they were present in the occipital areas; in others they were seen in the parietal and frontal areas only.

Dr. Gustav Bychowski: What changes were observed in the records of homosexual persons? I understand from Dr. Diethelm's personal communication that a number of the patients who were studied were homosexual.

Dr. Donald J. Simons: I cannot answer that question. Perhaps Dr. Diethelm has such information.

Dr. Oskar Diethelm: I omitted a discussion of homosexual patients. Some of them fell in the group of psychopathic personalities; in others the disorder was of psychoneurotic origin. The electroencephalographic patterns vary considerably and have not been studied sufficiently.

Dr. Harold G. Wolff: I should like to ask Dr. Pacella whether the disturbances described by Drs. Diethelm and Simons were in any way related to those he described in the records of his anxious patients at the last meeting.

Dr. Bernard L. Pacella: Apparently they are not. The patients who showed a great deal of anxiety often exhibited a prominent alpha rhythm. The waves sometimes were almost continuous, without the interruption of low voltage fast

activity, which is ordinarily noted between alpha "spindles." I might add that other subjects, who may have the usual amount of tension when coming into the electroencephalographic room, may reveal patterns which are in some instances similar to the tracings described by the authors for their psychopathic patients and which would ordinarily be considered normal. However, I believe that in the authors' records the waves had a significantly higher amplitude, which would then classify them as abnormal.

Natural History of "Sciatic Neuritis." DR. HENRY SHANKLAND DUNNING (by invitation).

In recent years a common neurologic disease called sciatic neuritis has been found to be caused, in the majority of cases, by herniation of the nucleus pulposus of a lower lumbar intervertebral disk with pressure on nerve roots of the cauda equina. I maintain that the symptoms and signs of herniation of the nucleus pulposus in the fourth lumbar or the lumbosacral intervertebral disk are indistinguishable from the well defined syndrome that was formerly called sciatic neuritis. Cessation of pain after removal of a herniated nucleus has been so impressive that whenever this characteristic syndrome appears the question of spinal operation demands consideration. However, cessation of pain has been observed without spinal operation with sufficient frequency to justify the supposition that the defect may be repaired by natural processes. In order to verify this supposition the present study was undertaken, which consisted in finding out what has happened to patients who had so-called sciatic neuritis before the operation for removal of the disk was presented.

Follow-up data were obtained on 55 patients with a condition which was reliably diagnosed as sciatic neuritis and which, after careful consideration of the symptoms and signs, would beyond reasonable doubt now be classified as probable herniation of the nucleus pulposus of the fourth lumbar or the lumbosacral intervertebral disk. Most of these patients were private and ward patients in the New York Hospital. All had pain in the posterior or posterolateral aspect of one leg which was increased by stretching the sciatic nerve of the affected leg. Additional symptoms and signs were pain in the lumbosacral region; tenderness in the region of pain; increase of pain by raising the intra-abdominal pressure, as in straining during defecation; diminished intensity or absence of the ankle jerk and weakness of muscles, paresthesia and decreased cutaneous sensation in the distribution of the fourth lumbar through the second sacral nerve root. The methods of treatment were numerous, but none of the patients had a spinal operation. The follow-up period began with the first attack of pain which was reliably diagnosed as sciatic neuritis and ranged from one year and three months to twenty-three years, with an average of five years and one month.

The patients were divided into the following groups on the basis of the follow-up data:

1. Patients who have been continuously free from pain in the leg and the lower part of the back since the subsidence of the first attack. The duration of pain in the leg ranged from eleven days to three years, with an average of seven months. The period of recovery ranged from one to seven years and eight months, with an average of three years and five months.

2. Patients who have had persistence, recurrence or development of pain in the lower part of the back since the subsidence of pain in the leg. Inconsequential and considerable degrees of pain were reported, but none of the patients mentioned disability from it.

3. Patients who have had persistence or recurrence of pain in the leg with or without pain in the lower part of the back. Three degrees of pain could be defined: inconsequential, and not interfering with former activity; considerable, but permitting relatively light work; disabling, or not permitting any material physical work. In the last category were placed the 5 patients who eventually

had a spinal operation, with resulting relief from pain in each case. In 3 cases the operation was referred to as "spinal fusion"; in 1, as "spinal operation," and in the last the operation is known to have been the removal of a herniated nucleus pulposus in the fourth lumbar intervertebral disk. The results of follow-up observation are shown in table 1.

The follow-up data offered an opportunity to determine whether the prognosis for so-called sciatic neuritis could be predicted from the abnormalities found on neurologic examination or lumbar puncture. The neurologic signs consisted of diminished strength or absence of the ankle jerk, muscular weakness and decreased cutaneous sensation. The only abnormality observed on lumbar puncture was an elevation of the total protein content of the spinal fluid. The incidence of these abnormalities in the patients for whom the prognosis was satisfactory was compared with the incidence in the patients for whom the prognosis was unsatisfactory. In the group with a satisfactory prognosis 50 per cent of the patients had an impaired ankle jerk; in the group with an unsatisfactory prognosis the incidence was 48 per cent. The incidence of muscular weakness and decreased cutaneous sensation was somewhat higher for the patients whose prognosis was satisfactory. In the group with a satisfactory prognosis the total protein of the spinal fluid

TABLE 1.—*Results for 55 Patients with "Sciatic Neuritis" Who Were Followed One and One-Fourth to Twenty-Three Years*

	Satisfactory		Unsatisfactory	
	Number	Per Cent	Number	Per Cent
Free from pain	20	36		
Pain only in lower part of back				
Inconsequential	2	4		
Considerable	..	..	2	4
Pain in leg				
Inconsequential	8	14		
Considerable	..	..	16	29
Disabling	..	..	7	13
Total	30	54	25	46

exceeded 45 mg. per hundred cubic centimeters for 8 of the 14 patients who had a lumbar puncture; in the group with an unsatisfactory prognosis it was elevated in 5 of the 12 patients who had a lumbar puncture. Thus, it appears that prognostic predictions cannot be based on the neurologic signs or on the protein content of the spinal fluid.

For the purpose of therapeutic evaluation, Dr. Bronson Ray has submitted his data in 100 cases at the New York Hospital in which he operated for removal of a supposed herniated nucleus pulposus in the fourth lumbar or the lumbosacral intervertebral disk. In earlier times the symptoms and signs in these cases undoubtedly would have led to the diagnosis of sciatic neuritis. The operative procedure and the lesions found at operation, with their incidence, were as follows: removal of a herniated nucleus pulposus, 76 cases; removal of an unherniated degenerated nucleus pulposus from a ruptured disk, 13 cases; decompression of nerve roots without removal of the nucleus pulposus from an incompletely ruptured disk, 3 cases; no diseased disk, 8 cases. In table 2, the results in 82 of these cases in which follow-up observations were made for six months or longer are compared with the results noted in follow-up observation in the cases in which no operation was performed.

Conclusions.—Of the syndrome formerly called sciatic neuritis, and now known in the majority of cases to be caused by herniation of the nucleus pulposus of the fourth lumbar or the lumbosacral intervertebral disk, the prognosis is satisfactory without spinal operation in 54 per cent of cases.

Although removal of the herniated nucleus promptly relieves pain and betters the prognosis by 32 per cent, natural processes should be given an opportunity to repair the defect before spinal operation is urged.

Neurologic signs and spinal fluid protein are of no prognostic value.

TABLE 2.—*Follow-Up Observations in Eighty-Two Cases of Herniated Nucleus Pulposus Treated Surgically*

	No Operation (55 Cases) per Cent	Operation (82 Cases) (Ray) per Cent
Recovery		
Residual symptoms	36	60
Inconsequential	18	26
Considerable	33	12
Disabling	13	2

DISCUSSION

DR. BYRON STOOKEY: Dr. Dunning has brought to our attention an interesting and intriguing problem, one that has been presented to all who were seeing cases of so-called sciatic neuritis ten years ago, before herniation of the nucleus pulposus was recognized. I am sorry to disagree with a good deal of what he has said. I am not at all in agreement that in the cases in which the condition was called sciatic neuritis the trouble was in fact herniation, for there are a large group of cases in which the symptoms, by all the tests I know, are identical with what I should call herniation; yet operation has failed to show herniation. What is the cause of the pain in these cases? The oxygen epidurograms, which my associates and I at the Neurological Institute find to be very satisfactory, better by far than the gas myelograms, show no herniation; but in a few cases the symptoms have been so definite and the signs so distinct that we felt we were justified in operating. Yet no herniation was found. We have another group of cases of what in former days would have been called sciatic neuritis and is today called herniation in which we have had a defect in the air column; yet at operation no herniation was found. In these two groups of cases the condition could certainly be called sciatic neuritis since we have pretty well demonstrated that it is not due to herniation. These cases, I think, belong to the group in which the patient gets well without operation. What the trouble is I do not know. I do know that there is a group of cases at the Neurological Institute of what we call gluteal myositis in which the patients get well with roentgen therapy. There are other groups of cases in which there are similar disturbances of the mechanism of the lower part of the back and the patients get well without operation. I think that if Dr. Dunning were to continue the interesting study he has made, and were to include cases in which he had established the diagnosis of herniation, either with air or with an opaque substance, and then were to make follow-up studies in these cases, as he has suggested, he would have a group comparable to that in which operation is employed. In other words, the question, I gather, is this: Why rush into operation, since formerly many of the patients got well and the outlook for them was satisfactory? I doubt very much that this attitude is valid. The only way to settle the question is to carry out conservative treatment in alternate cases of herniation in which the diagnosis is proved, so far as it can be proved, and to compare them with the cases in which operation has been employed. Personally, having seen the herniations at operation, it is inconceivable to me that the patients could recover with any conservative treatment, unless it be with some form of manipulation. I have a distinguished friend in the Washington University School of Medicine who has had sciatic pain, and he has a colleague who puts him through a maneuver that gives him relief, so that whereas he could not move before, within five minutes he can move. However, he got tired of going for treatments and

decided to have an operation. No herniation was found. He still has the pain and is most uncomfortable, but he is relieved by manipulation.

I should like to ask Dr. Dunning what form of treatment he would suggest for trial before one resorts to operation. My own impression is that if the diagnosis is established as well as one can establish it operation is indicated. I agree that cases of this type are not happy ones for the surgeon to encounter. I have had many failures—many cases in which I do not find herniation. I wish I were one of those neurosurgeons who have a 100 per cent record of successful removal. I am sure, however, that from the old group of disorders called sciatic neuritis one distinct condition, that is herniation, has been picked out. There remain other conditions in that group which need to be reclassified.

DR. BRONSON SANDS RAY: Dr. Dunning has compared his observations with the operative results in the first 100 cases of diseased disk in which operation was performed at New York Hospital; as he implied, but perhaps did not stress, in many of the 100 cases of so-called ruptured disk operation did not actually show herniation. Nevertheless, in some of the cases in which there was no apparent herniation degeneration of the disk was present, even old tears in the annulus fibrosus without any nucleus pulposus remaining. In other cases, as Dr. Stookey has implied, the surgeon is unhappy in finding nothing at all that can be diagnosed as disk disease. My notion has been, and I suspect that I have influenced Dr. Dunning somewhat in his attitude, that often when no frank protrusion of the disk is found at operation there is reason to believe that there has been disease of that disk which has served to change the local anatomic structure, if you like, and thereby to put the nerve root or roots in that region in such a position as to be easily injured by some motion or stress of the back. I have still considered such a condition to be a disease of the disk, and I believe that it would be entirely unfair to call it protrusion, or herniation, of the nucleus pulposus. Certainly, the problem is still a much debated one, and I agree entirely with Dr. Stookey that the surgeon does not have an easy time. He finds himself called on more frequently to account for the failures than he does to help celebrate the successes.

I believe that some of the patients Dr. Dunning included in his study had such a short illness that they would not have been considered subjects for operation. It may be that these patients with early spontaneous recovery would have a better prognosis than those who go on for some time before operation is performed.

DR. HENRY SHANKLAND DUNNING: Dr. Stookey asked me how I should treat patients who have this syndrome. I know of no better treatment than rest in bed and I suppose that, since patients firmly maintain the value of the device, they should rest on a bed board.

With respect to Dr. Ray's last comment, 1 patient who recovered had pain in the leg for only eleven days; the others were ill for longer periods, up to three years, the average duration being seven months.

DR. BRONSON SANDS RAY: Did any of the cases occur in the last eight years, since operative treatment has been in use?

DR. HENRY SHANKLAND DUNNING: Yes, indeed, many of them.

DR. HAROLD G. WOLFF: I think Dr. Dunning stated that seven months was the average time required for recovery.

DR. HENRY SHANKLAND DUNNING: Seven months was the average duration of pain in the leg in the group of patients who made a complete recovery after the first attack.

DR. HAROLD G. WOLFF: How does that compare with the period for the operative procedure, from the beginning of pain until the patient was back on the job?

DR. HENRY SHANKLAND DUNNING: When a patient has a protruding nucleus removed, the period is cut down to just the time of recovery from operation.

DR. HAROLD G. WOLFF: What are the facts, Dr. Ray?

DR. BRONSON SANDS RAY: I do not know that I can give figures, but I am sure the period of recovery would be under seven months.

DR. HAROLD G. WOLFF: Three months?

DR. BRONSON SANDS RAY: I should think so.

DR. A. M. RABINER: I am confused as to the purpose of this paper. Does Dr. Dunning mean to tell us that there is no such thing as sciatic neuritis, that all pain in the lower part of the back, of radiating character, is due to a slipped disk, or is he saying that all patients with sciatic pain which persists have herniated disk?

DR. HENRY SHANKLAND DUNNING: When a patient presents himself with the syndrome that used to be called sciatic neuritis, I have no way of telling whether it is sciatic neuritis or disk disease. At present patients are frequently urged to have an operation early in the course of the disease, whatever it is. I did not wish to give the impression that I think that in all these cases the pain is caused by disk disease.

DR. A. M. RABINER: You mean that you do not know whether there is such a thing as sciatic neuritis?

DR. HENRY SHANKLAND DUNNING: That is so.

DR. PETER G. DENKER: At Bellevue Hospital my colleagues and I face this problem frequently, and we have found it helpful to call in the orthopedists who, with their roentgenographic technic, provide objective evidence of disease of the disk. Dr. John McCauley, of the orthopedic department, has shown us cases in which by tilting the patient to one side and then the other the roentgenograms of the lumbar region of the spine showed absence of compression of the intervertebral space where the herniated disk was present. We have not found Dr. Stookey's procedure of injection of air of much help but have learned to place more diagnostic importance on elevation of the protein of the spinal fluid.

On the whole, we feel more optimistic about the surgical approach in these cases than would be indicated by the authors. It is my impression, after my experience with such cases in the past five or six years, that the neurosurgeons have a good deal to offer and that the results obtained have been far better than they were in past years, when the condition was always called sciatic neuritis and treated with rest and supportive measures.

I cannot help but comment on the title of this paper, which, in my opinion, could just as well have been called: "Natural History of Disease of the Intervertebral Disk." One must think of the latter entity as an illness with remissions, just as one thinks of multiple sclerosis or pernicious anemia in similar fashion. It is not at all unusual to see the patient recover from his first attack spontaneously; sometimes one even obtains a history of two or three attacks in the past. I therefore rarely advise operation during the first attack unless it is unusually severe or persistent. One cannot but be impressed with the fact that in these days a diagnosis of sciatic neuritis is made rarely, since it has come to be realized that in most cases the disease is really a traumatic lesion of the intervertebral disk with radicular symptoms of sciatic pain.

DR. BYRON STOOKEY: I should like to ask Dr. Denker whether, when he speaks of injections of air as being of little value, he has tried the epidurographic method, that is, the introduction of air outside the dura. We first used subarachnoid injections and found it very difficult to get an adequate picture of the area between the fifth lumbar and the first sacral vertebra; we got fairly good pictures between the fourth and the fifth lumbar vertebrae and excellent pictures above that; so we finally gave up that procedure and relied on the epidurogram. I wonder what Dr. Denker's experience has been with the epidurogram.

DR. PETER DENKER: We have not used the epidurogram; our injections have been subarachnoid.

DR. LEO M. DAVIDOFF: It seems to me that the cases Dr. Dunning has described are clinically so classically like the cases of herniated disk that certainly all of them certainly could not have been instances of conditions other than herniated disk; in other words, some of the patients must surely have had a herniated disk and have recovered. Therefore I cannot entirely agree with Dr. Stookey that the patients who improved had "sciatic neuritis" because of some other factor and for that reason got well without operation. We see patients who prove to have diseased disks who do get well, as in the cases Dr. Denker described. I know a man who had his first attack twenty years before a recurrence, and after the recurrence a ruptured disk was found at operation. His second attack was exactly similar to the one occurring twenty years before; therefore the question in my mind is not whether patients with herniated disk associated with the sciatic syndrome can improve but whether the improvement is permanent. I believe most of the patients will have another attack, and when they do they probably will have an operation. It is perhaps unwise to operate at the time of the first attack, and it is my attitude that when the patient is having his first attack, or has just had it, he should be left alone and then operated on when has a recurrence.

DR. HAROLD G. WOLFF: What is the rate of recurrence in the series at the New York Hospital?

DR. BRONSON SANDS RAY: I am not sure that I can give the figures, and I should want to qualify my answer by distinguishing between persons who have recurrent backache and those who have recurrent sciatica. I believe that the recurrence of pain in the back after an operation for injured disk is 40 per cent and that the recurrence of sciatic pain is approximately 10 per cent.

Acute Alterable States in Multiple Sclerosis. DR. C. RAY FRANKLIN (by invitation) and DR. RICHARD M. BRICKNER.

Several years ago a patient at the Neurological Institute had sudden, brief attacks of blindness. I observed pronounced spasms of his retinal arterioles during these attacks. Subsequently, I presented the case before the Section of Ophthalmology of the Academy of Medicine. The patient had disseminated disease of the central nervous system but not the typical syndrome of multiple sclerosis.

Within the past year Dr. Brickner and I have observed 13 patients with true multiple sclerosis who showed similar phenomena. Some were from Mount Sinai Hospital and some from the Neurological Institute. Some of them had sudden attacks, and others were still suffering from impaired vision of recent onset. Scotomas could be plotted; spasms of retinal arterioles could be seen, and both could be instantaneously relieved with injection or inhalation of vasodilator drugs.

In addition, 2 patients with multiple sclerosis with associated morning diplopia obtained instantaneous relief by inhaling amyl nitrite.

Another patient, with mild intention tremor, suffered a decided increase in the tremor on smoking a cigaret. This effect could be prevented by an intravenous injection of papaverine hydrochloride or by the drinking of liquor.

These observations led us to the hypothesis that there may be a connection between the arteriolar spasms and the symptoms and that the spasms may be the cause of the lesions in the nervous system. Whether this is true or not, under these conditions one is free from the problem of spontaneous remissions and other complex, long term characteristics of the disease. These are acute states, instantaneously alterable, and they furnish a condition in which isolated, controllable experiments can be performed. (Slides were shown illustrating (1) the arteriolar spasms [paintings]; (2) the scotomas immediately before and immediately after administration of the drugs; (3) diplopia before and after inhalation of amyl nitrite, and (4) straight lines drawn by the patient with intention tremor, showing the effects previously described.)

Comment.—We have not been able to study controls with diplopia and scotomas from other causes. Dandy has reported a case of aneurysm of the carotid artery in which ptosis was improved with cold baths. Shumacher and Wolff described transient relief of changes in the visual fields associated with migraine with small amounts of amyl nitrite.

We wish to mention a case of permanent hourglass spasms in which a paradoxic reaction occurred with use of vasodilators—the constriction became narrower and extended farther along the involved arterioles.

DISCUSSION

DR. HAROLD G. WOLFF: Can the authors draw any conclusions from these observations?

DR. RICHARD M. BRICKNER: Only those I mentioned: These observations led us to the hypothesis that there may be a connection between the arteriolar spasms and the symptoms and that the spasms may be the cause of the lesions in the nervous system. What impressed us was not that spasms and scotomas were present but that they were present simultaneously and could be reduced or abolished together. Dr. Rucker, at the Mayo Clinic, described spasms in two retinal veins, but he did not associate them with visual disturbances; we think that the spasms can be linked up with visual disturbances, a hypothesis which gives our observations their interest.

DR. LEON H. CORNWALL: Since 1913 a number of theories regarding the cause of multiple sclerosis have been advanced by numerous authors, including Gye, Marinesco, Kuhn and Steiner, Simons, Rothfeld, Freund, Hornowski, Brickner and Putnam. Strong evidence against its transmissibility by inoculation methods or against an organismal origin has been presented by a group of workers, including Siemerling and Raecke, Hauptman, Burley and Dudgeon, Magnus and Teague. The work of Teague seems to me to deserve more widespread notice than it has received. With the modesty which so often characterizes those who devote their lives to research, Teague considered his negative results as unimportant and never published them, except in a brief note in 1922. He devoted one year full time to an investigation of the disease. His work was done in the laboratories of the department of neurology, Columbia University, under a grant from the Commonwealth Fund. The material for his study consisted of injections of blood and cerebrospinal fluid from 16 persons suffering with multiple sclerosis, and these injections were made into a total of 219 animals—including guinea pigs, rabbits, 2 dogs and several monkeys. His conclusion was that there is no evidence to substantiate the belief that multiple sclerosis is due to a spirochete or to any other organism or that a disease with similar clinical symptoms can be transmitted to the animals that he used by the inoculation of blood or cerebrospinal fluid. Assignment of the pathologic examination of the material removed by Dr. Teague was made to me after Dr. Teague gave up this work. Briefly, there was no evidence of any lesions that resembled multiple sclerosis in any of the animals that he had inoculated.

In 1927 I injected cerebrospinal fluid from a patient with rapidly progressing multiple sclerosis into the lumbar sac of a Macacus rhesus monkey and at the same time injected fluid into a rabbit and a guinea pig. Observations on these animals revealed no evidence of disease after ten months. In 1930 Dr. Groszberg and I attempted to produce the disease in animals (rabbits) by the injection of blood from patients suffering from multiple sclerosis. When we terminated the experiments we had injected material from 23 patients into over 70 rabbits. As controls, the blood from presumably normal persons was injected into 20 rabbits. I shall not review that work now. The results were rather interesting but not particularly significant. It is true that the animals given injections of blood from patients suffering with multiple sclerosis manifested a greater incidence of symptoms indicating neurologic disease, but we did not feel that this had enough importance to warrant a report.

The same vascular phenomena responsible for the ocular changes in the 13 patients observed by Dr. Franklin and Dr. Brickner might, I think, play a role in the causation of multiple sclerosis. At least, such a speculation seems to me permissible. This appeals to me as much more reasonable than some of the other pathologic, physiologic and chemical observations which have been postulated as having a possible causal relation to multiple sclerosis. I do not know just what Dr. Brickner's attitude is now to the role of esterases in multiple sclerosis, nor do I know just how strongly Dr. Putnam feels that venous thrombosis in itself is causative, but it has been my personal feeling that the observations reported by these two workers are merely incidental, and not in any sense related to the fundamental cause or causes of this interesting disease. I do not know whether every patient with multiple sclerosis has an increased esterase content of the blood, and a somewhat similar remark might be made regarding the presence of venous thrombi. I do feel, however, that the observations that Dr. Brickner and Dr. Franklin have reported this evening may contribute to the discovery of the etiologic factor or factors more than anything that has preceded, and I shall be interested to hear Dr. Wolff's comments.

Dr. S. Bernard Wortis: I wonder whether Dr. Brickner has any cases of multiple sclerosis that he has studied in which these phenomena have not been found; also, has he observed these changes in the retinal vessels in patients with vascular disease without associated neurologic signs and symptoms?

Dr. Harold G. Wolff: I take it these patients have no other vascular disease —hypertensive or other arterial disease.

Dr. Richard M. Brickner: No; there was no evidence of other vascular disease.

Of the patients who did not show the spasms, some had no visual symptoms; others may have had visual symptoms and we missed the arteriolar changes. I defer to Dr. Franklin in the observations on the retina. I have thought that I saw beautiful spasms and have sent the patient to Dr. Franklin, only to be told that there was no spasm. Dr. Franklin has limited himself to changes in the vessels that are extremely definite, and any doubtful ones have not been included. Another point: Sometimes these phenomena are transient. They may be there for just a few minutes. I had a patient at Mount Sinai Hospital with visual symptoms that seemed to come and go; she was treated with histamine, and her vision was better after each infusion. I looked at the fundi, in company with Dr. Drooz, the resident in neurology; we each saw, independently, one vessel in the patient's retina which was opening and closing almost like a fist as we looked at it—Dr. Franklin has seen a number like that. I saw it first and asked Dr. Drooz to look, without telling him what I had seen; he saw the same thing. It was never observed again, and no other vascular abnormality has been seen in this patient's fundi.

Dr. Peter G. Denker: I should like to ask Dr. Brickner whether all these patients had diffuse lesions of multiple sclerosis or whether they represented cases of retrobulbar neuritis that was presumptively multiple sclerosis.

Dr. Richard M. Brickner: No, they were all cases of true multiple sclerosis except for Dr. Franklin's first case at the Neurological Institute. In this case there was diffuse disseminated disease of the nervous system, but not the kind of process which for these purposes we should call multiple sclerosis, although it probably is. There was a case at Mount Sinai, that of a youth of 17, who was there for the study of fever with hives; one day he suddenly declared that he was blind; several members of the house staff found a great blanching of one retina; I don't think there was time for any of the attending physicians to see it. He had a number of these attacks while in the hospital, and he has had about fifteen since. That was over eight months ago. There was nothing neurologic about the case, and we are interested in following the patient to see whether he ever does have multiple sclerosis.

Reactions Following Electric Shock Treatment. DR. JOHN FROSCH, DR. DAVID J. IMPASTATO, DR. LILLY OTTENHEIMER (by invitation) and DR. S. BERNARD WORTIS.

Electric shock treatment frequently produces clinical by-products of interest. Most frequent is the organic confusion which arises in the course of treatment and persists for some time afterward. We should like to call attention to another interesting clinical syndrome which we have encountered and which has been referred to in other reports. The treatments were given daily, and each patient received a preconvulsive intravenous injection of sodium amytal. Treatment was continued until the patient became confused and his clinical symptoms subsided.

Essentially, the picture consisted in an acute psychotic episode starting a few days after treatment was discontinued and lasting several days to several weeks. The reactions observed represented something more than the usual organic confusion which arises in the course of treatment and persists for some period afterward, It appeared that after treatment was discontinued the patient showed the usual memory defects and confusion, which differed little from the picture seen in our other patients. In a few of the patients in whom psychotic episodes developed the subjective reaction to the memory difficulties and confusion was more pronounced. A few days to a week after treatment was discontinued an acute psychotic picture developed, which lasted from a few days to a few weeks. These psychotic episodes took different forms, but all had in common the feature that the patient was disturbed, agitated, restless, assaultive and destructive, and occasionally stuporous. In some instances the patient was demanding, suspicious and paranoid. In the main, however, the gross clinical picture of the psychotic episode was different from the psychiatric picture seen before shock treatment was instituted.

That the development of the psychotic reaction did not have any direct correlation with the degree of confusion was also manifested by the fact that sometimes as much as a week elapsed after treatment was terminated before the psychosis developed. During this interval the confusion frequently lessened. It might well be that as the confusion subsided sufficiently the patient's awareness of his defects became more pronounced in those cases in which psychosis developed. It was as though the tolerance of the ego to the defects and to the distortions of the body image was not so good in these patients as in those who did not have the complication.

It appeared to us that the organic changes caused by electric shock were not entirely responsible for the development of the psychotic episodes. The fundamental personality structure in its reaction to the organic damage appeared to be important.

All the developing psychotic reactions subsided, and the most that happened was that the patient was left with his previous psychiatric picture. With the clearing of the engrafted psychotic picture most of our patients also showed improvement in their original clinical complaints. Once having discontinued shock therapy, one must wait, therefore, before reinstituting it when such a reaction develops.

DISCUSSION

DR. ROBERT B. MCGRAW: The title of this paper also is somewhat misleading. As a matter of fact, on reading the paper carefully one finds it is a discussion of a particular psychotic complication seen after a certain number of treatments of a certain character of depressed patients in the second decade of life. All these patients were subjected to in excess of ten grand mal seizures over a relatively short period, and most were given daily treatments. I mention the intensity of the treatment because work is being carried out with different modalities in an effort to produce seizures and to avoid, at the same time, the electroencephalographic abnormalities, or at least to keep them minimal. Even though I am not one to be much disturbed by the permanent damage to the cortex from electric shock and

am inclined to feel that memory disturbance is not entirely without benefit, I feel one should not allow the reactions to proceed too far, particularly in patients of the affective reaction type. Possibly my interest in ambulatory shock therapy has made for more conservatism, and I may have erred on the side of giving too little treatment; but I have had some patients who have recovered and maintained recovery with as few as three or four treatments, a fairly large number with five and many with six. All the patients reported on here received more than that. I believe that even for depressive reactions these patients were treated a bit too long and too frequently. The authors themselves suggest this, at least with respect to the daily treatments. Schizophrenic reactions may need more prolonged treatment, and manic excitements may do well with daily treatments for a short period. With the summary of the paper I am almost entirely in accord. The authors mentioned Dr. Kalinowsky's paper, given at Philadelphia. In that paper he emphasized organic factors in psychotic manifestations complicating electric shock treatment. In the present paper underlying personality factors and psychogenic factors are emphasized. There is no doubt in my mind that different people react differently to the same amount of memory change, even though this change may be fairly slight. The awareness of this change may come about some time after the treatments have been discontinued.

DR. OSKAR DIETHELM: While listening to this paper, I was reminded that at the First International Psychiatric Congress, held in 1924, after World War I, malaria treatment was presented, and great attention was paid to the fact that in a number of the cases of dementia paralytica in which cure was effected a paranoid picture developed. I remember that Bleuler arose and said that these reactions were manifestations of latent schizophrenia. When there was no longer much malaria treatment of severe dementia paralytica, these psychotic reactions became rather infrequent. I was also reminded that in 1936, when Dr. Joseph Wortis came back from Vienna, he told us about severe reactions to insulin treatment. He mentioned regression of the personality to the infantile stage. I mention this because such observations do not relate merely to electric shock treatment but seem to occur with two similar forms of treatment when far-reaching therapy is used.

DR. LOTHAR B. KALINOWSKY: Dr. Diethelm is correct in stating that similar reactions are also found with insulin treatment, though less frequently. They likewise occur with metrazol treatment. I think one must understand them, in the light of other symptomatic psychoses or organic reaction types, as occurring with infectious-toxic diseases or any other interference with cerebral function. In a paper presented before the American Psychiatric Association (Organic Psychotic Syndromes Occurring During Electric Convulsive Therapy, ARCH. NEUROL. & PSYCHIAT. **53**:269 [April] 1945), I tried to show that one sees in electric convulsive therapy the whole series of organic reaction types, from slight confusional states to severe Korsakoff syndromes, hallucinoses, delirium-like pictures and, finally, deep dementia-like states. When the patient comes out of a quiet confusion, he sometimes passes through a more productive state, as described by the authors. Organic reactions can be largely avoided by limiting treatments to two a week; but in hospitals these reactions should not be feared, for, as the authors pointed out, they always clear up in a week. It is of great interest to study the choice of symptoms. A psychoneurotic patient with a schizoid personality will more readily present a schizophrenia-like organic syndrome, with delusions and hallucinations, whereas a cyclothymic personality is predisposed to an organic reaction with manic-like or depressive features. Thus one can foretell from the patient's original personality what type of symptoms he will show. These observations during electric convulsive therapy confirm the view that the clinical picture of an organic reaction, i. e., the choice of symptoms, is not determined by the type of the noxious agent; in electric convulsive therapy the agent is always the same, and yet various patients present a great variety of organic syndromes. In accordance with obser-

vations on patients with other symptomatic psychoses, it seems that the same patient in several courses of electric convulsive treatment may react each time with the same clinical picture.

DR. S. BERNARD WORTIS: May I emphasize two points? First, I would speak a word of caution to persons using electric shock treatment; second, I wish to point out that this syndrome occurred in a patient who was given the treatment three times a week. The confusion alone is not productive of this particular psychotic reaction.

DR. HAROLD G. WOLFF: Do I understand that all these patients recovered?

DR. S. BERNARD WORTIS: Yes.

DR. DAVID J. IMPASTATO: It should be made clear that psychotic reactions following electric shock therapy are uncommon, and few patients have them. I have given treatments once a week, twice a week, three times a week and every day. Most of our patients have been treated twice a week. We now have over 400 patients who have been treated twice a week. Of these 400, only 1 had a psychotic reaction like that described this evening. In general, one may say that these psychotic reactions occur infrequently in patients treated once or twice a week and that most of them occur with the daily treatment. If you want to obviate them, do not treat patients daily.

Why are patients with depressions given daily treatments? Such patients were given daily treatments at Bellevue Hospital because we thought we might be able to shorten the period of hospitalization. We have found that daily treatment did not achieve this and have discontinued this regimen for depressions. We have obtained excellent results in treating depressed patients twice a week, and they should be so treated except perhaps at the beginning if the patients are suicidal or severely depressed, when treatment three or four times a week for the first week is indicated.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

MADELAINE R. BROWN, M.D., *Presiding*

Regular Meeting, Feb. 15, 1945

Histopathologic Effects of Anoxia on the Central Nervous System. DR. L. RAYMOND MORRISON and DR. STANLEY COBB.

This paper was published in full in the January 1946 issue of the ARCHIVES, page 1.

DISCUSSION

DR. C. G. TEDESCHI, New York: There is little that one can add to the discussion of a paper presented by Dr. Morrison and Dr. Cobb. Many years ago Dr. Cobb, at that time working in association with Dr. Gildea, showed that ten to fifteen minutes of practically complete cerebral anemia will induce permanent lesions. Later, other investigators, including Heymans and associates and Weinberger and Gibbon, showed that the lethal period is shorter by several minutes; and Sugar and Gerard, through electroencephalographic studies, demonstrated that the time required for the disappearance of potentials in the brains of animals with cerebral anoxia varied from ten seconds to two minutes in different parts of the brain of the same animal. Yet the classic description by Gildea and Cobb of the intimate neuronal changes accompanying the phenomenon of anoxia remains unchallenged. This evening Dr. Morrison and Dr. Cobb have taught us something more about cerebral anoxia—that it results in a process of intensive demyelination of scattered distribution. They have stressed the difficulty that they encountered in detecting the presence of fat in the affected areas of demyelination. I found

myself in the same difficulty not long ago while studying the brains of animals subjected to head trauma under various experimental conditions. Among the observed changes, moniliform swelling of the myelin sheaths and their breaking down, absorption and resolution into round, oval or irregularly shaped globules were frequently found. In these demyelinated areas, the sudan III and Marchi methods almost constantly failed to reveal the presence of fat droplets, and only in a few instances could droplets be seen in the oil red O preparations, with pyridine solvent. At that time Dr. Benda gave me an explanation of the phenomenon, and I am sure we will all appreciate hearing from him on this point.

Evidence of vascular injury, especially of the blood capillaries, has long been recognized as one of the most constant pathologic manifestations of death from asphyxia, and the members of this society remember the beautiful demonstration by Campbell, Alexander and Putnam of such injury in the brain substance. May I ask Dr. Morrison whether, in his opinion, the patchy distribution of the lesions he has shown is due to a vascular factor or to a difference in sensitiveness to the anoxic agent of the various areas of the brain?

There is another point I should like to bring up in the discussion. The occurrence of hyperglycemia during asphyxia and other conditions, such as emotional disturbances, has been known since the early investigations of Claude Bernard and has recently been emphasized by Britton, Hill and others. The increase in blood sugar in these conditions is thought to be due to an outpouring of epinephrine, which causes augmentation of the rate of hepatic glycogenolysis and discharge of sugar into the blood. May the cellular changes that the authors have just described and compared with the changes seen in fatigue be related to these metabolic disorders?

Dr. Clemens E. Benda, Wrentham, Mass.: It is hardly necessary to congratulate the authors on this paper, for every neuropathologist must have liked to listen to it. I wish to make one comment only on the changes in the myelin. There is no doubt from the slides presented that there is true degeneration of the myelin and that the paleness of the white matter is not artificial. I feel that it is not accidental that Dr. Morrison failed in his attempts to stain the broken-down myelin with fat stains. From my own material, as well as from the literature, I am under the impression that degenerated myelin gives a positive reaction to fat stains only if the myelin is catalyzed by action of other cells, whether nerve cells, glia cells or phagocytes. If free myelin is broken down without the action of cells, the broken-down material is not catalyzed to a state of neutral fats accessible to the so-called fat stains. The balls of degenerated myelin stain with various methods, but they are not broken down to the level of free fat. I should like to ask Dr. Morrison whether he has had the same experience.

Dr. L. Raymond Morrison: In answer to Dr. Tedeschi's question about the focal and general, widespread regions of demyelination, and as to whether I think there is a relationship between the focal types and the blood vessels, I do not know. I have frequently seen in my preparations that when the patch of demyelination was small it often had in its center a blood vessel, while in the extensive, widespread areas of demyelination there was no special relation to blood vessels.

I could have shown a few slides illustrating the increased cortical activity of the adrenal glands, which, as was shown by Thorn and his co-workers, is the basis of the mechanism for transforming proteins into carbohydrate. The association of hyperglycemia with anoxia is well known; and that was of great interest to me in the early days of this experiment, for I thought that if there were increased sugar in the blood and increased glycogen in the liver, since the brain metabolizes only glucose and since the amount of oxygen was cut down so that the brain could not oxidize all the glucose, there might be excess sugar in the brain. Therefore for a long time I looked for glycogen in the brain. It is hard to find glycogen. One has to work very fast. I could not use liquid air; the animals were too large to be decapitated. I froze the brain tissue in situ, fixed it in absolute alcohol in situ, and so on. After a while I learned that there is no excess glycogen there

under the conditions of anoxia, for the metabolic processes are reversed and anaerobic, instead of aerobic, glycolysis takes place, so that even more sugar is consumed than under normal conditions.

I am interested in Dr. Benda's information about the relation of fat in the tissues to the cell reaction. It seems good, and there must be something in it. As I think of some of my slides, the situation was precisely as Dr. Benda has stated.

Histologic Changes in the Brain Resulting from Various Anoxic Conditions. MAJOR F. H. LEWEY, Medical Corps, Army of the United States.

It is still an open question whether the effect of nitrous oxide and carbon monoxide on the brain is solely that of anoxia, or, in other words, is identical with that of high altitude. Histologic changes in the brain similar to those following anoxia were to be expected if this was the case. No studies directed along this line could be found in the literature.

The same problem exists with respect to the correlation between the degree of oxygen tension or concentration in the blood in various noxious conditions and the resulting damage to the brain. A correlation between the fortuitous circumstances of human pathology and specifically designed animal experiments must be effected to open an approach to these problems.

The brains which formed the basis of this study were those of 3 patients who died after exposure to nitrous oxide, carbon monoxide and strangulation, respectively. All 3 patients showed the same typical picture of decortication. Such patients cannot be kept alive longer than eleven days, even under the best nursing care. The material is, therefore, comparable clinically and with respect to the survival time. No data could be obtained concerning the concentration of carbon monoxide in the blood of 1 of the patients. Certain conclusions about it may be drawn from comparison with material gained in well controlled animal experiments.

The brains of the persons who had died of nitrous oxide and carbon monoxide poisoning showed extensive necroses, more pronounced in the cortex in the first and in the white matter in the second. In the former the glial reaction was prominent; in the latter there was no glial or mesodermal reaction. These changes were more intensive than those found in the average case of carbon monoxide poisoning in men, and comparable alterations are equally rare in experimental animals because animals so strongly intoxicated do not survive long enough to show histologic changes.

My experiments indicate that in dogs a histologic picture comparable to that described in man requires a concentration of carboxyhemoglobin in the blood of 90 per cent. To this end, dogs were intoxicated in a closed rebreather system with pure carbon dioxide mixed with oxygen until cardiac standstill occurred. The dogs were resuscitated by transfusion with oxygenated red blood corpuscles, in addition to artificial respiration.

Correlation of the histologic changes in the brain with the concentration of carbon monoxide in the blood of dogs suggested that 75 per cent carboxyhemoglobin represents a critical level below which even intoxication prolonged over many hours fails to produce pronounced changes, in contrast to the intense alterations of the brain tissue from short-lasting intoxications above that level.

Electrocardiographic and electroencephalographic tracings during prolonged carbon monoxide poisoning in dogs strongly suggest that the primary cerebral disturbance occurring with carbon monoxide poisoning is reversible and that the characteristic changes in the brain are secondary to the circulatory collapse.

The brain of the patient who tried to hang himself failed to show any histologic changes with the same magnification and staining methods as those applied in the cases of nitrous oxide and carbon monoxide poisoning. Finer methods of examination with higher magnification are needed to show the damage which is actually present. This mechanism is best visualized by staining the hemoglobin in the cortical blood vessels. Such slides indicate that certain cortical areas are void of circulation. The opinion that this phenomenon is caused by anoxia, and not by

interruption of circulation in the carotid arteries during strangulation, is strengthened by its duplication in another brain after death from pure anoxia corresponding to an altitude of 36,000 feet (11,000 meters). A further corroboration of the qualitative difference of the histologic changes in the brain following carbon monoxide poisoning, on the one hand, and pure oxygen deficit, on the other, was found in an experiment on two series of dogs, in one of which the animals were exposed to small doses of carbon monoxide and showed the typical changes in the brain, although of low grade. The other series, which was kept in the underpressure chamber for the same length of time in an atmosphere containing an even slightly lower partial oxygen pressure than that produced by the carbon monoxide, failed to show any histologic changes.

To sum up: The histologic changes in the brain following nitrous oxide and carbon monoxide intoxication in man are similar. Those following a corresponding degree of pure anoxia are different. This observation does not support the opinion that nitrous oxide and carbon monoxide act exclusively through the resulting anoxia. The varying histologic pictures following inhalation of carbon monoxide depend mainly on the degree of concentration of carboxyhemoglobin in the blood above 75 per cent. The direct effect of carbon monoxide, and possibly of nitrous oxide, on the brain seems to be reversible, whereas the well known pathologic changes appear secondary to the circulatory collapse following myocardial anoxia, which does not occur until a carboxyhemoglobin concentration of 75 per cent is reached.

DISCUSSION

DR. BRONSON CROTHERS: I should like to ask Major Lewey about the age of the patients. We have seen repeatedly, after accidents of birth or carbon monoxide poisoning, for example, children who have become completely decerebrated and idiotic. Apparently, in children under 4 years of age the percentage of fatalities is not nearly as great as among adults.

DR. C. G. TEDESCHI, New York: Major Lewey has already made other contributions to the field of cerebral anoxia and has shown that exposure over a long period to small amounts of carbon monoxide, generally considered within the safety limits, is far from harmless. In my opinion, the observations he has presented this evening are still more important, as they show that the histologic changes in the brain following exposure to nitrous oxide and carbon monoxide are different from those following a corresponding degree of pure anoxia. The most logical conclusion, as he stressed, is that nitrous oxide and carbon monoxide do not act exclusively through the resulting anoxia. Might I ask Major Lewey whether the observations on the brain were extended to the myocardium and, if so, whether a different pathologic process was displayed in the latter under the different anoxic conditions?

DR. JACOB E. FINESINGER: I should like to ask Dr. Lewey about that experiment in which carbon dioxide got in by mistake. What percentage of carbon dioxide is necessary in the breathing air to obtain a protective effect? What mechanism is active in protecting the animal from the effects of anoxia?

MAJOR F. H. LEWEY, Medical Corps, Army of the United States: Dr. Crothers' question is pertinent. Puppies with anoxia behave very differently from adult dogs. Kabath and his co-workers found that young animals survive longer periods of anoxia than do older ones.

In reply to Dr. Tedeschi's question: The pathologic examination of hearts was confined to cases of death from carbon monoxide. Multiple hemorrhages into the heart muscle, especially the papillary muscle, were noted. Such changes were reported by Klebs as far back as 1865.

In reply to Dr. Finesinger's question, I refer to the experience that hemoglobin becomes progressively less able to hold oxygen as carbon dioxide increases in the blood. In other words, the oxygen dissociation in the blood is facilitated by increased carbon dioxide tension in the blood.

MADELAINE R. BROWN, M.D., *Presiding*

Regular Meeting, March 15, 1945

Pathologic Changes Associated with Injury to Nerve Induced by Cold. DR. D. DENNY-BROWN, DR. RAYMOND D. ADAMS, DR. CHARLES BRENNER and MISS MARGARET M. DOHERTY.

The results of two series of experiments were reported, both of which were carried out on cats. In the first series, the sciatic nerve was exposed aseptically and a length of 1 cm. packed off and frozen solid with a spray of carbon dioxide. After a variable period the frozen part of the nerve was thawed by the application of a cool or tepid isotonic solution of sodium chloride. On the day after the operation and at intervals thereafter the animals were examined to determine the degree of motor and sensory paralysis. When the animals were killed, motor responses to faradic current applied above and below the lesion were noted. The nerves were stained with a variety of histologic methods to demonstrate myelin, fat, axis-cylinders and cells.

In the second series, cooled brine at a constant temperature ranging from —4 to + 3 C. in various experiments was circulated through a small cylindric metal jacket surrounding a segment of sciatic nerve (20 mm.) for a measured time (usually two hours). The temperature of the brine was determined by thermometers at the inflow and the outflow and the temperature of the interior of the nerve by a fine thermocouple inserted between the fasciculi of the nerve. As with the first series, the animals were killed after varying periods of survival and observation and the nerves examined microscopically after suitable fixation and staining.

It was found that the myelin and axis-cylinders were selectively damaged by exposure to cold, the largest fibers being the most sensitive and the smallest the least sensitive. Damage to the large motor fibers and the fibers conveying sense of contact was produced by exposure to temperatures as high as + 8 C. for intervals as short as thirty minutes. The mildest degree of damage resembled that produced by transient ischemia, but the severe lesion differed in that destruction of myelin in the affected fibers was complete without the smallest fibers necessarily being damaged. The affected myelin underwent dissolution. Necrosis of whole bundles of nerve fibers occurred only after freezing. Regeneration was rapid and complete in all grades of injury short of complete necrosis.

DISCUSSION

CAPTAIN JAMES C. WHITE (MC), U. S. N. R.: I thought that my best contribution to this presentation of the effects of cold in experimental animals would be to tell of my experiences with immersion foot in the Navy. In a tour of special duty to Halifax, Nova Scotia, and during the past three winters at Chelsea, Mass., I have had an opportunity to study about 100 cases of the early or late stage of these lesions which result from exposure to cold water. For descriptive purposes, it is best to divide them into two distinct stages and to talk about each stage separately.

In the early stage one finds lesions very similar to those described in the authors' experimental animals. These consist of an inflammatory reaction, with discoloration of the skin, swelling and hyperemia. There are changes in the superficial blood vessels and a progressive paralysis of the subcutaneous nerves from the ankle down to the toes. Pain, burning in character, is usually present as soon as the extremities warm up and continues until the inflammatory reaction subsides. (Colored lantern slides and charts were shown to illustrate these points.)

In the late stage the presenting symptoms and signs are caused by contraction of fibrous tissue. There is necrosis of the skin, intrinsic muscles and supporting structures of the foot, with loss of mobility and clawing of the toes. The nerves have more or less regenerated, and it is very painful for the patients who have been most severely exposed to walk. Lieut. Comdr. Shields Warren, patholo-

gist to the First Naval District, and I have studied a series of biopsy specimens obtained from such patients. (Lantern slides of the photomicrographs were shown.) There is a striking increase in the intercellular fibrous tissue. This is limited almost entirely to the collagen, and the number of fibroblasts is not particularly increased. The subcutaneous nerves are embedded in this fairly dense fibrous tissue. Three months after exposure some of the nerves still show edema and a slight degree of wallerian degeneration. Many of the arterioles and venules are partially to almost completely occluded as a result of the great increase of fibrous tissue within their walls. Biopsy of muscles shows an easily appreciable fibrosis and atrophy of the striated fibers.

From this study we have derived the impression that much of the late pain has been due to perineurial fibrosis. It tends to subside after six to eight months, at which time the collagen ceases to contract. There are also several other factors which deserve mention. Pain is frequently a by-product of nerve regeneration. Sir Wilfred Trotter has discussed this in an essay on the effects of loss of insulation (myelin) in damaged nerve fibers. Such fibers have lost their normal conduction and respond only to painful stimuli, and then in an explosive, exaggerated way. Owing to the infiltration of the subcutaneous tissues and intrinsic muscles with fibrous tissue, the finer arterioles are also constricted, and circulation is thereby reduced. This suggests the postulate that painful metabolites are removed more slowly and are therefore an added cause of the pain which appears so consistently on walking. The periarticular and peritendinous fibrosis, with added atrophy of the intrinsic muscles and ligaments which give mechanical support to the feet, is a third factor which I should like to call to your attention as important. Taken all together, these factors constitute a satisfactory explanation of the long-standing pain which may be such a disabling condition in shipwrecked mariners who have been adrift for long periods in cold water.

DR. D. DENNY-BROWN: In beginning the investigation, it seemed to us that the great problems concerned with this condition centered around (1) the extreme liability to pain in the late stages and (2) the great delay in recovery of motor function. The delay was satisfactorily explained by Blackwood and Russell, who showed that the muscle undergoes direct necrosis and that that presumably leads to the fibrosis of which Captain White spoke.

The painful vasoneuropathy is not peculiar to this condition. It is seen with various kinds of peripheral neuritis. It was therefore of some general interest to find that the smallest nerve fibers, the sympathetic and pain fibers, escape. The idea that hyperesthesia can result from isolation of pain sensation from other forms of sensation is not new. Regeneration is not impeded, provided there is not complete necrosis.

Penicillin Treatment of Neurosyphilis: A Preliminary Report on Seventy Patients Followed from Four to Twelve Months. DR. AUGUSTUS S. ROSE, DR. L. D. TREVETT, DR. J. A. HINDLE, DR. C. PROUT and DR. H. C. SOLOMON.

During the twelve months ending Feb. 1, 1945, 106 patients with symptomatic neurosyphilis were treated with penicillin at the Boston Psychopathic Hospital. The diagnoses for the 70 patients who have been followed for four to twelve months are as follows: dementia paralytica, 49; tabes dorsalis, 6; atrophy of the optic nerve, 6, and chronic meningovascular syphilis, 9. Treatment consisted in sixty intramuscular injections of 50,000 Oxford units of penicillin (total 3,000,000 Oxford units) given concurrently or in succession with one-half the usual amount of therapeutic fever in the form of malaria or fever cabinet therapy. Seven patients were treated with penicillin alone. The time interval of the injections of penicillin varied, a series of cases being collected in which injections were given (1) every four hours, (2) every three hours, (3) every two hours and (4) every hour.

The over-all clinical results at the time of this report show that of the 70 patients, the condition of 28 is improved, that of 37 is unchanged and that of 5 is worse.

Of the 49 patients with dementia paralytica, 25 show improvement and 21 no change and 3 are worse. Thirteen of the patients with dementia paralytica had been committed to state hospitals for mental disease for four months or longer. The results for the remaining 36 patients are striking: 24 show improvement and 11 no change, and 1 is worse. Five of the 6 patients with atrophy of the optic nerve have an apparent arrest in visual loss.

In a satisfactory percentage of cases the spinal fluid shows a return of the cell count and the total protein content to normal and a gradual decrease in the titer of the Kolmer-Wassermann test. Study of the results for 30 patients treated by older methods reveals a comparable alteration in the spinal fluid. In many of the previously untreated patients with dementia paralytica an immediate reaction consisting in increase in the cells and the protein content of the spinal fluid with intensification of symptoms was noted.

Of the total of 106 patients, 7 have died. Two of these demonstrated that penicillin cannot be counted on to alter beneficially the terminal phase of dementia paralytica, and the question is raised as to the advisability of using this drug in the overactive end stage.

DISCUSSION

DR. RAYMOND D. ADAMS: I know of only one previous study in which an attempt was made to evaluate the penicillin treatment of neurosyphilis. That came from the clinic of Dr. John Stokes, of Philadelphia, and was published in *The Journal of the American Medical Association* (Stokes, J. H., and others: The Action of Penicillin in Late Syphilis, **126**:73 [Sept. 9] 1944). Dr. Stokes and his associates observed the effects of penicillin on 180 patients with late syphilis, 122 of whom had neurosyphilis. Penicillin was given intramuscularly, and in a few cases intravenously, in amounts varying from 600,000 to 4,000,000 Oxford units. Improvement in the cerebrospinal fluid occurred in 70 per cent of patients; the cells disappeared, and the total protein and the titer of the Wassermann test were reduced. Clinical improvement was noted in approximately 80 per cent of 40 patients with dementia paralytica, in 20 per cent of patients with tabes dorsalis and in 65 per cent of patients with meningovascular syphilis.

A neurologist reading the report of Stokes desires clarification of several points. It is not clear just what methods of treatment were used and what results they produced. For example, it is said that some patients were given penicillin and some fever therapy, but further details were omitted. It was said that clinical improvement was not always accompanied with improvement in the cerebrospinal fluid, but no attempt was made to correlate these factors. It was not defined what constitutes improvement in some types of neurosyphilis. For instance, how does a patient with meningovascular syphilis show improvement—by partial or complete restoration of function after a stroke or by the prevention of other vascular lesions? Of course this paper was written in the first flush of enthusiasm for the new method, and many omissions are to be expected; it serves as a stimulus to the study of penicillin in the treatment of neurosyphilis.

The paper presented tonight and that of Dr. Stokes indicate that the abnormalities in the cerebrospinal fluid are unquestionably influenced by penicillin therapy. Dr. Rose's caution in advocating the wholesale use of penicillin in treatment of dementia paralytica and in abandoning tried and proved methods is laudable. Syphilis is a chronic disease, and years are required to evaluate properly any therapeutic method. The methods now in existence are based on twenty or thirty years' accumulated experience. So with penicillin a long period of intensive study will be necessary before its place in therapeutics can be assigned.

It is well to remind persons not working in this field of some of the major difficulties encountered in the treatment of neurosyphilis. Older methods of treatment, which include the use of trivalent arsenicals and bismuth, fever and tryparsamide, are fairly effective. When they are used in cases of the latent and asymptomatic disease, the development of serious late forms of neurosyphilis can usually be prevented. Some of the difficulties encountered in the application of existing

methods may be noted. 1. Most patients who come to a neurosyphilis clinic did not know before that they had syphilis, and therefore they have never been treated for the disease. Dr. Merritt and I looked over our rather large material at the Boston City Hospital and found that about 80 per cent of our patients did not know they had syphilis and had never had any treatment until neurologic symptoms developed. The remainder had received only very inadequate treatment. This explains why present therapeutic methods have not significantly reduced the incidence of neurosyphilis. This difficulty actually reduces itself to the problem of case finding. The only solution lies in the routine serologic testing of blood for syphilitic reagin, in making lumbar punctures in all cases of latent syphilis and in treating the patient until the cerebrospinal fluid is normal.

2. Existent methods of treatment require time and the cooperation of the patient. He must come to the clinic week after week. In the clientele of a large city hospital, which includes many itinerants, psychopaths and the like, it is difficult, even with the assistance of a social worker, to maintain faithful attendance at the clinic and thus to provide adequate treatment. Of 250 of our patients with asymptomatic syphilis, only 100 received enough treatment to bring about a serologic reversal of the cerebrospinal fluid.

3. Older methods of treatment when applied intensively over a short period and fever therapy carry some risk, especially for elderly people with complicating diseases.

For these reasons, syphilologists seek new drugs which are safe and quick acting.

The investigation which Dr. Rose and his association have presented is a conscientious and sober evaluation of the treatment of dementia paralytica with penicillin. In a way, it is unfortunate that fever therapy, even in reduced amounts, had to be given with the penicillin treatment, but the reasons are obvious. What is needed, of course, are many more patients with asymptomatic neurosyphilis and early dementia paralytica treated with penicillin alone and observed carefully for a long period.

I wish to ask several questions: 1. Have the authors determined the concentration of penicillin in the cerebrospinal fluid? Keefer and Anderson showed that penicillin does not enter the cerebrospinal fluid from the blood stream and suggested that the drug has to be given intrathecally if it is to be effective. Other workers pointed out that in cases of meningitis, in which exudation occurs, penicillin reaches the cerebrospinal fluid in sizable quantities. Is it necessary to have a high level to achieve a good result? If so, will it become necessary to give the drug intrathecally?

I know of Dr. Solomon's reluctance to admit that any real Herxheimer reaction occurs in the cerebrospinal fluid. How does he regard the intensification of symptoms mentioned in this report? Is there any risk in injecting a large amount of penicillin into an untreated patient? Is there any danger of producing transverse myelitis or a vascular lesion?

Dr. William R. Hill: My associates and I have used penicillin at the Massachusetts General Hospital since September 1943 in treatment of patients with primary and secondary syphilis, all of whom had active lesions from which spirochetes morphologically consistent with Treponema pallidum were obtained. Our method of treating these patients has been to hospitalize them and treat them with intramuscular injections of 20,000 units every three hours for seven and a half days, for a total of 1,200,000 units. There was one interesting observation. Four of the patients experienced a pronounced Herxheimer reaction after the second dose. They had a temperature of 103 and 104 F. and suffered severe pains in the back and chills. We continued, however, to give penicillin at regular intervals of three hours, and the symptoms subsided, without residuals. We believe there is no danger in continuing penicillin therapy under these conditions. The Wassermann reaction of the blood became negative in thirty to seventy days in the majority of cases, and active lesions resolved in three weeks. We studied the spinal fluids of all our patients before treatment and found them to be normal. In a recent lecture

Moore stated that 20 per cent of a large group of patients with early infectious syphilis had a serologic or clinical relapse within the first year. Now a plan is being set up to increase the effectiveness of penicillin with a rapid course of treatments with arsenicals or fever.

DR. HARRY C. SOLOMON: First, I shall try to answer Dr. Adams' question. I suppose I am a bit stubborn about the Herxheimer reaction. The phenomenon may be due to the killing of spirochetes, but there may be something else involved. Some form of exacerbation is present in the central nervous system of these patients. The cell count rises characteristically in all cases in which this treatment is used.

The question whether penicillin alone would be adequate in treating dementia paralytica is not answerable at this time; Dr. Hill has pointed out that in cases of early syphilis in which penicillin is of proved value relapses are not as infrequent as one would like. At any rate, there are a number of clinics where the drug is being used as the only treatment, and their results will elucidate that point without our aid. Hence, we have kept on with what we should ordinarily consider an inadequate course of fever therapy in conjunction with the use of penicillin. Four or five febrile bouts do not take much out of the patient. They do not leave him "washed out" and weak. They can be given at the same time that the penicillin therapy is being carried on. The general evidence is that penicillin becomes more effective with each degree of rise in body temperature. Whether with fever the penicillin is broken down or eliminated so rapidly that an adequate blood level is not maintained we do not know.

Whether penicillin should be given intrathecally has been considered. We decided to get as much information as possible about the intramuscular method before trying the intraspinal route. Some have used the intrathecal method, but it has not been proved very definitely that it is more beneficial.

There is one observation of mine that may not be accurate. Dr. Rose has presented the statistical data on the effects of treatment and has pointed out the dramatic improvement of patients with dementia paralytica when they receive ten or twelve treatments of fever. This dramatic, sudden improvement seems to be less frequent with penicillin therapy. I think we have seen no resulting hallucinations, such as one finds in the treatment of dementia paralytica with malarial fever alone. If this method of induction of small amounts of fever with malaria combined with penicillin therapy is as effective as a long course of fever treatments followed by a long course of chemotherapy, then it is a great advance. At the present time it looks as though we were getting very good results. We still have many variations to consider. We have been using 3,000,000 units as the total dose. Should we use a different amount, say 6,000,000? What about the period between treatments—one, two, three or six hours? Should penicillin therapy be combined with chemotherapy? Should intrathecal injections be given? Should one give longer courses of fever and penicillin therapy, with the expectation of getting better results than with either method alone? These are some of the aspects of the problem which are before us.

To answer Dr. Adams' question as to the penicillin in the cerebrospinal fluid: We have not set up requirements for the recovery of penicillin. The procedure is not difficult but is somewhat complicated. Such a determination has not been made. We do not have any information on the matter, nor does any one else. One does not have to find the penicillin in the spinal fluid to prove that the drug is useful. The amount of arsenic in the cerebrospinal fluid is not related to its effectiveness. So we are not unduly concerned about its determination in the fluid.

DR. ALFRED HAUPTMANN: I have only one question: Can Dr. Rose tell us about the changes seen at autopsy in the brains of the 7 patients who died? I am especially interested to know whether there were changes from the histologic picture of dementia paralytica to that of meningovascular syphilis. Viennese investigators found such changes after treatment with malaria. This means a change from an ectodermal to a mesodermal reaction.

DR. AUGUSTUS S. ROSE: We believe that this sudden increase in cells and protein and the temporary intensification of symptoms occur only in cases in which the patient had not received recent antisyphilitic therapy. It does not occur during the second course of penicillin treatments. These facts indicate that the reaction has something to do with the activity of the disease.

DR. JAMES B. AYER: I was particularly impressed with the success in treatment of primary atrophy of the optic nerve, for this serious condition has not in my experience yielded to any other form of treatment.

With reference to the cell count as indicative of pathologic activity, I would remind you of an early article by Dr. Solomon in which he stated that cells were sparsely present in the spinal fluid and yet at autopsy many cells were found enmeshed in the subarachnoid space.

DR. AUGUSTUS S. ROSE: We do not have data regarding the type cell which is liberated. The intensification of symptoms argues for a temporary increase in the inflammatory process rather than a flushing of the perivascular spaces of the cells.

The 6 cases of atrophy of the optic nerve were clearcut. All the patients received injections of penicillin and treatments in the fever cabinet. All had determinations of the visual fields and visual acuity at frequent intervals. One showed progression of visual loss. In 2 of the remaining 5 patients vision seems to have improved. Their visual fields are questionably wider. There may be some improvement in acuity. We realize that partially blind patients often have subjective improvement while under active treatment; so we make no claims. In all 6 cases the atrophy of the optic nerve is apparently of the typical syphilitic primary form. In none was there evidence suggesting atrophy of the optic nerve due to basilar meningitis. A recent preliminary report from another clinic participating in the investigation of the Office of Scientific Research and Development indicates that their results in cases of primary atrophy of the optic nerve are approximately the same.

ILLINOIS PSYCHIATRIC SOCIETY

DAVID SLIGHT, M.D., *President*

Regular Meeting, March 1, 1945

Spain as the Cradle of Psychiatry. DR. PETER BASSOE, Chicago.†

It is generally believed that there was no humane treatment of the insane in Europe until Pinel broke their chains, one hundred and fifty years ago. However, Pinel himself pointed to the fact that in Spain numerous good institutions, humanely administered, were founded in the fifteenth century. This is amply confirmed by German medical historians. Thus, A. Schmitz, writing in 1884, stated: "Not Pinel, but physicians in Valencia in 1409 were the first to remove chains and institute moral treatment." Ullersperger, in his book on early Spanish psychiatry (Die Geschichte der Psychologie und der Psychiatrik in Spanien von den ältesten Zeiten bis zur Gegenewart verfasst, Würzburg, A. Stuber, 1871), says that the cradle of psychiatry was in Spain and that "earlier than other nations, the Spaniards constructed convenient and appropriate buildings, the first real hospitals for the insane in the world." However, a recent Spanish writer, Gorriz, makes the statement that the first to break the chains of the insane was Cælius Aurelianus, who lived in Carthage in the second century A. D. As a matter of fact, the stimulus to the kind treatment of the insane in Spain came from the Arabs, who, again, had received theirs from the ancient Greeks, whose writings they copied in profusion and

† Dr. Bassoe died Nov. 5, 1945.

furnished to libraries in North Africa and the then Moorish Spain. While Christians in Europe generally looked on the insane as possessed of demons, the Mohammedans, not stressing the devil, treated them as sick people. Thus, in the thirteenth century patients in the asylum at Cairo were soothed by harmonious music and entertained by story tellers, dancing and light comedies. The more important early Spanish psychiatric literature was reviewed, as well as the writings of the philosopher-physician Maimonides and the psychologist Luis Vives and those by and about the novelist Cervantes, and their psychiatric implications.

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DISCUSSION

DR. FRANZ ALEXANDER, Chicago: In this most interesting, scholarly essay, Dr. Bassoe has come to a convincing conclusion concerning the claim expressed by several authors that Spain, and not France, should be considered the cradle of modern psychiatry. By a critical study of historical sources, he has confirmed the fact that the humanization of the treatment of psychotic persons started earlier in Spain than in other European countries and that Pinel, by removing the chains from the insane, only repeated what more than three hundred years before had been accomplished in Spain. On the other hand, together with other cultural achievements of Spain, this progressive attitude toward the mentally sick, as well as some valid descriptions of psychotic conditions, became lost to the rest of Europe, and only after their rediscovery in other countries did these achievements exert an influence on the development of psychiatric thought. A glance at the general contours of European history furnishes the answer to the question why early attainments of Spanish culture did not further develop in Spain itself and could exert influence on the shaping of European destiny only after they were transplanted to other countries.

From the eleventh century until the death of Philip II, in 1598, Spain was one of the focal points of European development. During these centuries she was the standard bearer of Christianity against Mohammedan expansion. With the victory of Lepanto, Philip II conclusively sealed the destiny of Islam in Western Europe. At the same time, Spain became the moving spirit of the counterreformation. In its fanatic defense, she became the leading European power, and the militant church, in combining feudal romantic chivalry with fanatic Catholic devotion, became a grandiose historical force.

Spain in the sixteenth century was the most powerful remaining citadel of medieval Catholicism in Europe and gave to its spirit in the persons of Loyola, Philip II, Saint Theresa, El Greco and Cervantes everlasting expression. In the counterreformation, led by Spain, medievalism made a last and tragic dying effort to stem the tide of the new era. Eventually, the spirit of romantic chivalry, mysticism, faith and passionate devotion had to yield to the victorious onslaught of modern rationalism. The spectacular rise and rapid downfall of Spanish hegemony over Europe belong to the most dramatic periods of history. Spain owes much of her greatness, but also her downfall, to her leadership in the counter-reformation. Her economic, political and spiritual disintegration had begun already under Philip II's reign and reached rapid completion under his two successors.

Historians of the nineteenth century often speak of the isolation of Spain within Europe. Ullersperger, one of Dr. Bassoe's sources, quotes a French historian in saying that "Spain is the least known of all countries of Europe; some islands of Oceania are better and more completely explored." These historians obviously refer to Spain after the seventeenth century. *Sic transit gloria mundi!* Spain, which in the sixteenth century made such a deep imprint on European customs, social forms, dress and also spiritual outlook, soon became the "forgotten man" of Europe, together with many of her cultural contributions. Early achievements in psychiatric practice and knowledge are only one of the many treasures buried under the ruins of modern Spain.

Spain's tragedy was that at the dawn of the modern era, unlike England, she failed to ride the "wave of the future." As a result, the first country to benefit from colonial expansion—which itself was the fruit of the adventurous awakening spirit of the Renaissance—she was also the first of the new national states to lose her influence in the European concert of powers. The hidalgo, with his adventurous inclinations, was possibly an able conqueror, but with his anachronistic ideology he was certainly not so well prepared to become a successful colonizer as the Dutch or the British trader. The genius of Spain was not in this field. Cervantes himself, on the basis of his pitiful record as a public administrator, was unable to obtain a governmental job in the Spanish colonies and thus was forced to continue his unsuccessful efforts to earn his living from writing. While Spain's early psychiatric achievements, in the technical sense, were lost, to be excavated five hundred years later as curiosities by modern medical historians, Cervantes' contribution to the knowledge of man's nature survived in a most dynamic fashion. *Don Quixote's* singular appeal to the young and old of all nations through three hundred years has been the topic of innumerable publications, only equaled by those about *Hamlet,* sharing with the latter the first place as the most profound portrayal of the universal conflicts of man. A short discussion cannot do justice to this masterpiece, the first psychologic novel of literature; but I should like to call attention to a few outstanding points.

It is customary to consider the story of *Don Quixote* as a masterful parody of contemporary Spanish society, particularly of the deteriorating hidalgo, the exponent of the small nobility, who no longer had a place in changing society and lived a shadow existence on the memories of past glory. Cervantes' father, Rodriquez, was a typical case, constantly fighting against his creditors by insisting on the privilege of a hidalgo not to be jailed for failing to pay his debts. Cervantes himself fought against the Mohammedans in the service of the king and lost the use of his left hand from wounds received in the battle of Lepanto. In literary criticism, as in every other field, there are the so-called realists, who can see only the obvious and are insensitive to those overtones which make the difference between ordinary literary production and a masterpiece. It is, of course, obvious that *Don Quixote's* tragicomedy is the symbolization of the dying Spanish culture in the sixteenth century. The perceptive eyes of the great writer foresaw in a sense the fate of a nation which, like its grandiose exponent Don Quixote de la Mancha, turned its face toward the past and in vain tried to keep alive the feudal ideology of romantic chivalry and militant religion, which, no matter how noble and inspiring, were doomed and had to yield their place to the new realistic orientation. However, the story of *Don Quixote* is more than contemporary satire. It is no secret with whom Cervantes' heart is; all his sympathy is with Don Quixote, the foolish knight, who, in spite of all his insanity, becomes the martyr of his idealism and the symbol of the higher strivings of man, while reason is represented by the faithful, but so utterly banal, Sancho Panza. However, reason survives and Don Quixote dies, and all feel sad and poorer after his departure. This universal effect on all readers shows that the tragedy of Don Quixote is not merely the local, time and space bound, tragedy of Spain, but is that of all man. To turn away from frustrating and drab reality by regressing to the colorful imagery of the past is a fundamental psychodynamic principle. This regressive trend, in different degrees, is present in every healthy or sick person. Psychotic symptoms do not follow psychologic principles different from normal processes. There is no special physiology for healthy and another for pathologic processes of the body; and, similarly, there are not two kinds of psychology, one valid for the healthy and one for the neurotic and psychotic mind. The basic principles are the same in psychology and in psychopathology. It is no accident that a Spaniard of the sixteenth century was the first to make the escape from the unbearable present into imagery of the past the central theme of a novel and to understand the paramount significance of regression in psychosis. Shakespeare and Cervantes died in the same year. Both anticipated science by three hundred years in bringing nearer to one's understanding

the baffling irrationality of the disturbed mind. Shakespeare succeeded in awaking one's compassion for the compulsive doubter, whose scruples and indecision provoke in the ordinary man—and even in the physician—nothing but impatience and irritation. Cervantes' achievement from the psychiatric point of view is even greater; he succeeded in awaking one's sympathy and empathy for the raving paranoiac by his instinctive understanding of his psychosis as a regressive retreat from reality into phantasy. For the psychiatrist, it is of special interest to note that Don Quixote and Sancho Panza are, like Don Juan and Leporello, complementary figures, personifying the two aspects of one and the same person. Most psychotic persons, apart from their autistic attitude, retain a certain amount of practical sense, which enables them to move around in the world. They live a double existence, retaining a tenuous practical relationship to the world, overshadowed by the self-created world of phantasy. Sancho Panza is the personification of the subordinated reason, helping his master, by taking care of his practical needs, to live by his folly. Only together, in their fascinating symbiosis, do Don Quixote and Sancho Panza—really one person—give a faithful picture of the paranoiac personality.

In a sense, psychosis and psychoneurosis are the most human of all diseases. Every animal can have stomach or heart trouble, but only in extremely rudimentary form a neurosis or psychosis. Phantasy, the faculty of imagining, is the basis of thinking which enables man to master his environment better than any other living organism. In psychosis this faculty is abused, not for mastering but for escaping from the reality which has overpowered the mentally sick. Perhaps this is the main, but hidden, reason that one cannot forgive the psychotic person. Because he abuses the most distinctive faculty of man, society has stigmatized him for centuries. Cervantes made a good case, in fact, the best possible case, for the psychotic person, demonstrating so effectively the extenuating circumstances in his favor. The ideals and principles of Don Quixote were lofty indeed, and, in a way, one cannot help admiring his tenacity in trying to live up to them. One regrets that life does not allow him to live the exemplary life of a knight errant. It is difficult to laugh at and despise him—the most one can say is that he was not for this world—he was too good for it. Is this not true also for many patients? Understanding the psychotic personality is the way of overcoming the stigma of mental disease. Perhaps it is not a coincidence that Spain, the first country to remove the chains from the psychotic patient, produced the man who was the first to understand him.

Behavior Problems in an Army Service Forces Training Center. CAPTAIN LEO A. KAPLAN, Medical Corps, Army of the United States.

The problems of behavior disorders in an Army Service Forces training center were considered from the standpoint of their importance not only for the present but for the future. I refer particularly to simple adult maladjustment, mental deficiencies, chronic alcoholism, constitutional psychopathic states and malingering. As psychiatrists we have long recognized the almost hopeless and ever increasing burden persons suffering from these disorders place on themselves, on their families and on society in general. My assignment in the service has placed me in a position to study these persons over a period of fourteen months in an Army Service Forces training center.

The psychopaths more or less retain their civilian pattern of behavior in the Army and as a group are incapable of attaining satisfactory adjustment. It has become apparent that all efforts at their rehabilitation are unsuccessful. Rehabilitation has had a fair degree of success with persons who are recidivists but whose past personality is free from psychopathic tendencies. (Examples of various bizarre behavior problems were discussed, and the histories of some malingerers were given.)

It is the general consensus that the majority of guardhouse prisoners, i. e., the psychopathic, the alcoholic and other mentally ill persons, should never have been inducted into the military service. On the other hand, to reject these persons or to return them to civilian life obviously creates resentment and poor morale in the

soldier who is conscientious and willing to make sacrifices. Most important is the ultimate effect on society. The old proverbial expression "survival of the fittest" becomes a paradox. The mentally and physically adequate youth of the nation are becoming invalids by the hundreds of thousands, whereas remaining behind are the psychopathic, the alcoholic and the other mentally unfit, who will continue to display their asocial and antisocial behavior—economic burdens to society and financial drains on the Government.

It is my personal opinion that it has been an error in judgment not to consider this fundamental proverbial saying, "survival of the fittest." The great postwar problem will be the same old question, only ever increased, "What shall we do with the psychopath?"

DISCUSSION

CAPT. CHARLES O. STURDEVANT, Medical Corps, Army of the United States: When the psychiatrist is confronted with the particular group under discussion, the problem of making a diagnosis is often difficult. For a long time I have been concerned in the making of any psychiatric diagnosis and have tried to hew to a rather rigid line in my discussion of this subject with other medical officers. As a member of many disposition boards, it has fallen to my lot to explain some of these diagnoses to other officers. I have felt that we psychiatrists are in need of a different sort of terminology. We are calling many things "psychoneurosis" in the Army as a matter of convenience, and I think it is true also in designating the psychopathic personality. I am sure that I have made mistakes of that kind in order to get rid of a man who was giving trouble within the command. At one time I suggested putting all such men in one company for special duty and training, as Dr. Kaplan indicated has been done in other countries. In England such groups are called "pioneer battalions," and they perform labor, often in combat areas.

My initial experience with the problem came in connection with Selective Service, when Dr. Harry Stack Sullivan visited the West Coast to set up standards for selection. Then it seemed that 25 per cent of the rejections should be for psychiatric reasons. My associates and I attempted to follow the standards, rejecting 25 per cent; but soon local directives stated that there were too many psychiatric rejectees, and the number dropped to 10 per cent. I think the problem of demand often determines the role of the psychiatrist in many induction stations.

In discussing the psychopathic soldier, the question was raised, "What about the French Foreign Legion, an army composed of psychopaths, distinguished fighters, and considered to be very brave?" Dr. Sullivan's comment was that perhaps we should be able to get some of these egocentric fellows to the battle line but there would be so much trouble involved that the whole army would be worn out before they began to fight. This certainly has been my experience.

Another factor concerned with this group is that the psychopathic soldier is extremely hard on the morale of any unit. The medical officer, and the psychiatrist in particular, is often confronted with the problem of discharging some person whom he feels is definitely psychopathic. The social history will support his view, but the commanding officer, when confronted with this decision, may object because he fears it will encourage others to seek discharge. I remember an instance in which regulations of the War Department permitted certain men of a certain age to leave the service. After a month or two the order was rescinded, and for several months afterward there was an epidemic of certain types of "discharge blues."

The problem of psychoneurosis in the Army is probably best handled through correct orientation and early evaluation, as is done in replacement training centers. The technics vary a great deal. Recently I have had an opportunity to review various plans in use and have found that psychiatric planning is rather individual. In one place they have set up what is called an advisory system. In another camp they may give orientation lectures; another has a mental hygiene director who is responsible to the commanding officer of the camp. All these plans seem to work rather effectively. One of the most useful programs in military neuropsychiatry is that of the division psychiatrist. His men are different from Dr. Kaplan's. The

division psychiatrist works with psychopaths, orienting them, assisting the command in classification and assignment, trying to teach them what psychologic adjustment in the Army should be. By the time they arrive at a port of embarkation these men are pretty well known to the psychiatrist. He knows whom he wishes to take, who he feels can tolerate the rigors of combat and who may have difficulty in the future. Perhaps he can carry one or more of the psychopaths into battle.

Cross Section Perspectives of Current Psychiatric Cases at the Juvenile Court. DR. SAM I. STEIN, Chicago.

Among personality problems of children is that complex known as delinquency. This is a legal, rather than a psychiatric, classification. This and other behavioral disturbances occurring in children are distinguished from those of adults mainly for academic, rather than clinical, reasons. Basically, no causal or etiologic separation can be made, for differences in child and adult personality problems are mainly in the outward manifestations or the visible and invisible symptomatology. A cross section appraisal of delinquency could be substituted for a cross section appraisal of seemingly different psychiatric segments. Correct answers in diagnosis and therapy for juvenile delinquency should have universal application in psychiatry's entire sphere of interest and competence.

Twenty-two cases are cited which are truly representative of various types encountered among the 1,000 or more children studied annually. Ample identifying material is given to place the patient in the most appropriate of three broad causal categories: somatogenic, or disturbances due to visible or invisible lesions of tissue structure; psychogenic, or disturbances due to intrinsic inhibition or emotional immatureness, and sociogenic, or disturbances due to poor or improper conditioning. Accordingly, this representative psychiatric problem is not covered by the wide base of psychosomatic medicine but is included in the still broader field of socio-psychosomatic medicine.

Just as in other medical disciplines, wherever feasible, treatment should be directed toward the cause of the ailment and symptomatic manipulations resorted to only when there is no practicable alternative. The human problem today is beyond the stage at which preventive measures alone will give needed results in the time available for interrupting the natural process of morbid psychogenesis. Specified features of treatment appropriate to each major causal category are discussed. Emphasis is placed on the extreme need for testing the probable specific of psychotherapy, which is described in the text as an attribute of energy. The idea of such a phenomenon is supported by Sherrington.

Men speak of needing more freedom in the social scheme. Actually, man is unprepared even to legislate freedom until he has freed himself of his emotional immatureness, which implies intrinsic insecurity, irrational aggression and selffish, subjective motivations and which causes him, through seemingly indisputable rationalizations, to wittingly or unwittingly enslave others in the widest range of manners, from that of fondly infantilizing a child to that of ruthlessly forcing another into compulsory servitude. Psychiatry is seriously in need of the "specifics or the common denominators" of psychotherapy, not only to help resolve the problems of delinquency but, in view of the unpredictable state of human affairs, to assist in waging successful, psychologic peacefare.

Book Reviews

Personality Factors in Counseling. By Charles A. Curran, Ph.D. Price, $4. Pp. 287. New York: Grune & Stratton, Inc., 1945.

This book is the work of a Catholic clergyman who has had psychologic training. Bishop Ready, of Columbus, Ohio, has written a brief preface, and Prof. Carl R. Rogers, of the University of Chicago, gives an interesting introduction to the subject of counseling. Dr. Curran has attempted to "analyze the inter-related functions and attitudes revealed in the personality during the process of adjustment." He states that definite therapeutic gains can be achieved with the technic of "non-directive" counseling, in which the counselor acts as a passive agent and makes no attempt to direct the client toward goals.

The greater part of this book is devoted to an elaborate and detailed statistical analysis of the case report of a single patient. Twenty interviews were phonographically recorded, and typescripts thus obtained were independently analyzed by several psychologists, with surprisingly consistent results. The relationship between client and counselor was carefully controlled in an attempt to place on the client the entire responsibility for the solution of his problems. Client attitudes were rated by means of (1) interview content analyses, in which arbitrarily chosen categories of negative and positive emotional responses and chance responses were tabulated by three observers, and (2) problem-solving analyses, in which a list of individual problems facing the client was made up at the start of the interviews and followed through to the last interview in order to evaluate the function of insight in the process of therapy. The relations between 1 and 2 were plotted diagramatically by means of insight evaluation charts.

In his summary, Dr. Curran agrees essentially with the earlier results of Rogers, Snyder and others and states that "the ability to make independent choices and put them into practice brings the client much greater self-confidence and happiness and he no longer feels that he needs help."

The last part of the book, entitled "Implications for a Philosophy of Personality," deals with the possible application of counseling to individual and social betterment.

This book is a valuable, accurate and stimulating work and should serve to promote interest in the application of objective methods of research to psychologic interviewing technics. Dr. Curran has carefully presented and analyzed his material and has a wide knowledge of academic psychology. The applicability of this method to psychotherapy, however, is subject to questioning, in the reviewer's opinion. The approach to the client is of necessity on a very superficial level, no attempt being made to investigate the unconscious factors underlying the neurotic symptoms. The author carefully avoids more than passing reference to freudian or other psychotherapeutic concepts in his dscussion of the benefits of counseling. The term "non-directive" may be disputed also, in that any interview situation implies considerable rapport between subject and examiner and it is practically impossible to avoid "directing" the client along certain lines of thought. The author's assumption that "the ability to solve his own problems lies within each individual" and is a function of the "responsible dignity of human nature" may be valid in cases of simple social maladjustment, such as that of Alfred analyzed in this book, but it has little scientific value when one is dealing with treatment of the psychoneuroses, which may require many months of "active" psychotherapy by trained psychiatrists before any improvement occurs.

Unfortunately, a case history prior to the interview is not given, so that the medical reader is unable to make his own judgment or diagnosis and hence cannot evaluate the results of the interview "therapy."

This book is recommended to persons interested in objective methods of psychologic research applied to the special field of counseling. It is also of interest to psychiatrists in that it offers a possible method of statistical evaluation of the "productions" of patients, the interpretation of which heretofore has been left largely to individual judgment.